FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

Arthritis Drug Advisory Committee

Discussion of Biologics License Application 125293, Krystexxa, (Pegloticase), Savient Pharmaceuticals,Inc., as a Therapy for Patients with Refractory Gout

Tuesday, June 16, 2009

8:30 a.m. to 3:30 p.m.

HILTON - WASHINGTON, D.C.

8727 Colesville Road

Silver Spring, Maryland

Food and Drug Administration (FDA)

Center for Drug Evaluation and Research (CDER)

Arthritis Drug Advisory Committee

June 16, 2009

Hilton Washington DC/Silver Spring, Maryland

Meeting Roster

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Food and Drug Administration (FDA)

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Arthritis Drug Advisory Committee

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Meeting Roster (continued)

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Food and Drug Administration (FDA)

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Meeting Roster (continued)

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Food and Drug Administration (FDA)

Center for Drug Evaluation and Research (CDER)

Arthritis Drug Advisory Committee

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Meeting Roster (continued)

FDA (Non-Voting)

Curtis Rosebraugh, M.D., M.P.H

Director, Office of Drug Evaluation II

CDER/FDA

Bob Rappaport, M.D.

Director, Division of Anesthesia, Analgesia and

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CDER/FDA

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Rosemarie Neuner, M.D., M.P.H.

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Food and Drug Administration (FDA)

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Arthritis Drug Advisory Committee

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Agenda

8:30 a.m. Call to Order

Kathleen O'Neil, M.D.

Introduction of Committee Chair, AAC

Conflict of Interest Statement

Nicole Vesely, Pharm.D.

Designated Federal Official

8:45 a.m. Opening Remarks

Jeffrey Siegel, M.D

Clinical Team Leader,

Division of Anesthesia,

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Products, CDER/FDA

The committee will discuss biologics license application (BLA) 125293, KRYSTEXXA (pegloticase), Savient Pharmaceuticals, Inc., as a therapy for patients with refractory gout.

8:50 a.m.	Sponsor Presentation Savient Pharmaceuticals, Inc.	
Introduction	Steven Hamburger, Ph.D. Group Vice President, Quality and Regulatory Affairs	
Treatment Failure Gout	Michael Becker, M.D. Professor Emeritus of Medicine University of Chicago Pritzker School of Medicine	
Efficacy	Vibeke Strand, M.D. Clinical Professor, Adjunct Division of Immunology/Rheumatology Stanford University	
Safety	William Schwieterman, M.D. Independent Consultant Cardiac Evaluation of Pegloticase	

	William B. White, M.D. Professor of Medicine, Calhoun Cardiology Center Director, Clinical Trials Unit, University of Connecticut School of Medicine
Risk Mitigation	William Schwieterman, M.D. Independent Consultant
Risk/Benefit	Michael Becker, M.D. Professor Emeritus of Medicine University of Chicago Pritzker School of Medicine

Food and Drug Administration (FDA)

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Agenda (continued)

10:20 a.m. Questions from the Committee to the Sponsor

10:40 a.m. Break

10:55 a.m. FDA Presentation BLA 125293 KRYSTEXXA (pegloticase) for Treatment of Refractory Gout
Rosemarie Neuner, M.D., M.P.H.
Clinical Reviewer,
Division of Anesthesia, Analgesia and Rheumatology Products,
CDER/FDA

11:40 a.m. Questions from the Committee to the FDA

12:00 p.m. Lunch

1:00 p.m. Open Public Hearing

2:00 p.m. Questions to the AAC and AAC

Discussion

4:00 p.m. Adjourn

C O N T E N T S

P R O C E E D I N G S

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DR. O'NEIL: Good morning. I would like to welcome everyone to this meeting of the FDA Arthritis Advisory Committee. And I would like to begin by asking the panel to introduce themselves, if we could start at the far end.

DR. BURLINGTON: Good morning. I'm Bruce Burlington, industry representative to drug safety and I'm a consultant.

DR. ROSING: I'm Douglas Rosing and I work at the National Institutes of Health.

DR. KAUL: Sanjay Kaul. I'm a cardiologist at Cedar Sinai Medical Center in Los Angeles; professor, UCLA School of Medicine.

DR. O'NEIL: If the people on the panel could please turn off their microphones after they have spoken, that will help. Thank you.

DR. PACKER: I'm Milton Packer, cardiologist, University of Texas, Southwestern Medical Center, Dallas.

DR. WILLIAMS: Jim Williams. I'm a

rheumatologist at the University of Utah.

DR. WEISMAN: Michael Weisman, a rheumatologist at Cedar Sinai Medical Center in Los Angeles.

DR. FURBERG: Curt Furberg, cardiovascular epidemiologist from Wake Forest University.

DR. NELSON: Lewis Nelson. I'm an emergency physician and medical toxicologist at NYU in New York.

DR. OLSEN: I'm Nancy Olsen. I'm a rheumatologist and I'm at University of Texas, Southwestern Medical Center in Dallas.

DR. O'NEIL: I'm Kathleen O'Neil and I will serve as your chair today. I'm a pediatric rheumatologist at the University of Oklahoma.

DR. VESELY: Nicole Vesely, Designated Federal Official, Arthritis Advisory Committee.

DR. MIKULS: Ted Mikuls, rheumatologist from the University of Nebraska.

DR. STINE: Robert Stine, statistician from the University of Pennsylvania.

DR. BUCKLEY: I'm Lenore Buckley. I'm a rheumatologist from Virginia Commonwealth University in Richmond, Virginia.

MS. ARONSON: Diane Aronson. I'm the consumer representative, from Cambridge, Massachusetts.

DR. CLEGG: Daniel Clegg, rheumatologist, University of Utah.

DR. NEOGI: Tahina Neogi, rheumatologist and epidemiologist from Boston University.

DR. NEUNER: Rosemarie Neuner. I'm the medical officer and reviewer for this application.

DR. SIEGEL: I'm Jeffrey Siegel, clinical team leader in the Division of Anesthesia, Analgesia and Rheumatology Products at the FDA.

DR. RAPPAPORT: Bob Rappaport. I'm the director of that division.

DR. ROSEBRAUGH: Drug Rosebraugh, director, Office of Drug Evaluation II.

DR. VESELY: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are

quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

For the conflict of interest statement,

the Food and Drug Administration is convening today's meeting of the Arthritis Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 12 of the Federal Food, Drug and Cosmetic Act, are being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special

government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves biologics license application 125293, pegloticase, Krystexxa, sponsored by Savient Pharmaceuticals, Inc. through licensing agreements with Duke University, the original developer of the recombinant porcine uricase enzyme, and Mountain View Pharmaceuticals, Inc., developer of the PEGylated technology, as a therapy for patients with refractory gout. Krystexxa is a registered trademark of Mountain View Pharmaceuticals, Inc.

This is a particular matters meeting during which specific matters related to Savient's pegloticase will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Bruce Burlington is participating in this meeting as a nonvoting industry representative

acting on behalf of regulated industry. His role at this meeting is to represent industry in general and not any particular company. Dr. Burlington is an independent pharmaceutical consultant.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all the participants to advise the committee of any financial relationships that they may have with any firms at issue.

We also just wanted to make a note that the patient representative was unable to attend the meeting at the last minute. Thank you.

DR. O'NEIL: Thank you. Next, we will hear some opening remarks from Dr. Jeffrey Siegel,

the clinical team leader, Division of Anesthesia, Analgesia and Rheumatology Products at CDER.

DR. SIEGEL: Thank you, Dr. O'Neil.

Good morning and welcome to this meeting of the Arthritis Advisory Committee. The FDA has convened this panel to seek input on the biologic license application for pegloticase, or Krystexxa, for the treatment of uricemia in patients with treatment refractory gout.

We'll begin the presentations with a presentation by the sponsor, Savient Pharmaceutical. They'll discuss the clinical development program for pegloticase and provide their assessment of safety and efficacy of the product. Then you will have a chance to ask clarifying questions of the sponsor.

After that, there will be the FDA presentation. The FDA does not contest the sponsor's view of this efficacy of pegloticase. Therefore, our presentation on the efficacy will be brief. Instead, we'll focus the bulk of our presentation on safety issues that have come up in

our review of the application for pegloticase.

These safety issues focus on several areas. The first is that we observed a higher rate of cardiovascular serious adverse events with pegloticase-treated patients compared to control. In addition, pegloticase is immunogenic. That means that giving the product causes antibodies to develop in patients receiving it. There's a higher rate of infusion reactions in patients receiving pegloticase and we will discuss those infusion reactions and possible cases of anaphylaxis in patients receiving pegloticase.

Following the FDA presentation, you'll have a chance to ask clarifying questions of the FDA presenter. Then, after an open public hearing, there will be general discussion and we'll ask you to discuss several questions. We'll ask you to consider the overall safety of pegloticase, the question about a possible cardiovascular safety signal. We'll ask you to discuss, overall, the clinical utility of a product like pegloticase, and, finally, to give us

your views overall on the risk-benefit and considerations regarding whether pegloticase should be approved.

Because of the issues concerning cardiovascular safety and the hypersensitivity reactions, we've asked members of the Cardio-Renal Advisory Committee to participate in this meeting, as well as members of the Drug Safety Advisory Committee, and we greatly appreciate the participation of these members.

I'd like to take this opportunity before we begin to thank all members of the panel for your willingness to participate in this important process and we greatly look forward to hearing your input. Thank you.

DR. O'NEIL: Thank you.

Next, we will move on to the presentation of the sponsor, Savient Pharmaceuticals, and the first speaker will be Dr. Stephen Hamburger.

DR. HAMBURGER: Good morning, Madam Chair, members of the Arthritis Advisory Committee, and the Food and Drug Administration.

My name is Stephen Hamburger. I am Group Vice President of Quality and Regulatory Affairs at Savient Pharmaceuticals. Thank you for giving us the opportunity to present pegloticase as a new treatment option for patients with treatment failure gout.

The proposed indication for pegloticase is use in patients with treatment failure gout. There are no effective therapies for this crippling and disabling orphan disease. Pegloticase enzymatically consumes uric acid, reducing hyperuricemia, and, thus, controls or improves the signs and symptoms of gout, including reduction of tophus burden, reduction of chronic pain, improvement of physical functioning, and decreased frequency of gout flares.

The Phase 2 program identified two dose regimens to further explore in Phase 3. While these two dose regimens were studied in Phase 3 and will be presented today, we propose that the preferred dose regimen is pegloticase 8 milligrams per deciliter administered intravenously every two

weeks, which we believe is safe and effective for patients with treatment failure gout.

There have been several important regulatory milestones in the development of pegloticase. These include the orphan drug designation for pegloticase for patients with treatment failure gout in whom conventional therapy is medically contraindicated or has been ineffective.

While the original IND submission was submitted in November 2001, the Phase 3 clinical program consists of two replicate studies initiated after FDA approval using the special protocol assessment process. Before these studies were completed, the FDA approved the statistical analysis plan. An ongoing open label extension study has allowed correction of long-term safety data and durability of response and symptom data.

In April of last year, we had a productive pre-BLA meeting with FDA personnel. Many key items were discussed, including the FDA request for Savient to provide open label

extension study data in the BLA. We have provided data on 121 subjects continuously exposed to pegloticase for 12 months.

The original BLA was submitted last October and soon thereafter, the FDA assigned the BLA priority review status. We submitted an amendment in February, which included an independent blinded cardiovascular adjudication report and clarification of our risk minimization plan originally provided in the BLA.

Other amendments to the BLA included the 120-day safety update and a blinded independent EKG evaluation. Thus, the PADUFA date is August 1st.

Today, our presentations will follow this agenda. Dr. Becker from the University of Chicago will further describe the crippling and disabling aspects of treatment failure gout. Dr. Strand from Stanford University will present the efficacy data from our Phase 3 program. Dr. Schweiterman will present the safety data on pegloticase. Dr. White from the University of Connecticut will

present the report from the blinded independent adjudication of cardiovascular events.

Dr. Schweiterman will present our draft risk minimization plan. And, finally, Dr. Becker will conclude our presentations with a benefit-risk summary of pegloticase.

In addition to the presenters, these Savient colleagues are with us today to answer any of your questions, as well as a number of experts in various scientific disciplines. The names and affiliations of these outside consultants are briefly listed on this slide.

In a few minutes, Dr. Becker will provide an overview of treatment failure gout. Gout results from an accumulation of monosodium urate crystals after prolonged period of hyperuricemia. In humans, purines are metabolized to uric acid via the intermediates, hypoxanthine and xanthine.

The aim of urate-lowering agents is to reduce circulating levels of urate. Allopurinol and febuxostat inhibit xanthine oxidase, thereby reducing uric acid synthesis. In all mammals,

except humans and great apes, uricase is present. Uricase is unique, as it enzymatically converts urate, which is poorly water soluble and has limited urinary excretion to allantoin.

While this uricase dramatically increases uric acid, its use is limited due to its short half-life and immunogenicity to the uricase protein. This prevents this product, rasburicase, to its use in chronic and acute use for only five days.

PEGylated uricase was designed to maintain dramatic decreases in uric acid and will improve the immunogenicity profile, allowing for chronic use. In summary, today, our presentations will show that patients with treatment failure gout are medically contraindicated for conventional drugs and, therefore, they need new therapeutic options, like pegloticase.

Again, thank you, and we look forward to answering your questions following our presentations. The next speaker is Dr. Michael Becker, who will discuss treatment failure gout.

DR. BECKER: Dr. O'Neil, members of the committee, ladies and gentlemen, at a previous Arthritis Advisory Committee meeting, Dr. Jack Cush and I presented independent evaluations of the status of gout, looking, in the broad sense, at the 5 million individuals affected by this disease. We agreed in those discussions that there was an unmet medical need for additional urate-lowering drugs to resolve the hyperuricemia and maintain normal serum urate levels in individuals affected by gout to prevent crystal deposition and the consequence symptoms of gout.

Today, I'd like to direct our attention to a similar unmet medical need, one in a much smaller segment of the population of gout, approximately 1 percent of patients with this disorder; and I refer to treatment failure gout, which I regard as an outcome of progressive gout that's characterized by painful arthritis and chronic inflammatory arthropathy, the accumulation of urate crystals to tophaceous deposits, which may become destructive and compressive, impaired

quality of life and chronic disability, and a consequence of intolerance or refractoriness to current urate-lowering therapy.

I should also add, and we will document, that patients with treatment failure gout have high incidences of co-morbid cardiovascular and metabolic disorders that complicate gout therapy and increase the underlying risk for disability and death.

This slide is offered to portray gout as a progressive process and explain how patients with treatment failure gout reach their level of affliction. Gout arises among approximately 15 or 20 million persons in the United States whose serum urate levels are persistently above the 6.8 milligrams per deciliter, the limit of urate solubility.

Only about a third of these individuals will ever progress to crystal deposition and clinical symptoms derived from the crystal deposition in the form of gout flares. Thus, of the 4 to 5 million people affected by gout at some

point, about three-fourths of these individuals will suffer recurrent flares, the development of tophi, uric acid stones in the urinary tract, and have reasons to undertake urate-lowering therapy.

This is usually undertaken with allopurinol in the United States, occasionally with uricosuric agents, like probenecid. And the good news is that over the course of many months to several years, the vast majority of affected patients with gout show resolution of their symptoms, a slowing down of attacks in number and eventual cessation of attacks, resolution of tophi, if they're present, a cessation of stone formation.

These individuals are successfully treated with oral agents. On the other hand, there are about 10 percent of patients in whom urate lowering is undertaken who have gout that can be referred to as resistant. These individuals have poor urate control and many have progressive symptoms.

I would point out, however, at the

current status of practice in America, that many of these individuals, in fact, most of them, by far, can be managed by adjustment of their urate-lowering medications or the addition of appropriate prophylactic medication to prevent the flares, which compromise urate-lowering adherence.

There still remain, however, about 1 percent of patients with gout whose failure to control urate is on the basis of intolerance or refractoriness to the current urate-lowering agents, and it's these individuals, by and large, who go on after a number of years to chronic arthropathy, tophaceous gout, and have disability and loss of quality of life.

A word about allopurinol. This has been the mainstay of urate-lowering therapy since its introduction in the 1960s. Allopurinol is approved for use at 100 to 800 milligrams per day. On the other hand, 95 percent of dosing in the U.S. is documented to be at 300 milligrams per day or less, even though many gout patients do not achieve a goal serum urate range below 6

milligrams per deciliter even at 300 milligrams per day.

The factors that contribute to the low dosing of allopurinol include intolerance in about 10 to 15 percent of individuals. Allopurinol intolerance is usually mild and readily reversible. But in approximately one in 1,000 or one in 2,000 patients, there are rare and sometimes life-threatening cutaneous reactions or hypersensitivity syndromes that are worrisome to the practicing community.

Dosage reduction is recommended in patients with impaired renal function, and it is another factor contributing to the underuse of allopurinol. And, finally, there are minimal randomized control trials that demonstrate the safety and efficacy of allopurinol at doses in excess of 300 milligrams per day.

I would also point out, again, that the clinical benefits of allopurinol and its sister xanthine oxidase inhibitor, febuxostat, require months to years of treatment to manifest

themselves.

In this slide, I'd like to compare baseline demographic or gout characteristics and co-morbid features in patients with gout and treatment failure gout. Among the baseline characteristics that we will show you, the comparison will be between patients enrolled in the recent febuxostat-allopurinol comparative studies, which represent a broad range of gout patients, and, in the additional columns, two groups, one from an observational natural history study of patients with severe gout, enrolled nine years ago in an observational trial of one year duration, and the population of treatment failure gout patients in the pegloticase development program.

With regard to the baseline characteristics, one can see large differences in the gout features. For example, patients in the natural history and pegloticase studies, patients with severe or treatment failure gout have much higher frequency of active flares. The flares

occur many more times per year than in the broader population of gout. These patients have frequent arthropathy. By that, I mean tender and swollen joints that are ongoing, an unusual feature between flares in most patients with gout. They have approximately a threefold increase in the prevalence of tophi.

Among co-morbidities, patients with treatment failure gout have increased rates of cardiovascular disease, hypertension, advanced stages of renal impairment, diabetes, and hyperlipidemia.

In the natural history study that I referred to before, 110 subjects with severe gout were chosen by academic investigators and their disease was characterized in much the same way that the patients selected for the pegloticase development program chose patients. In this case, however, the limitation on serum urate was that they not have achieved urate levels in the treatment range.

The important thing about this study is

that disability and quality of life was measured in these patients and, in fact, higher disability scores and impaired quality of life correlated with the higher rate of gout flares, a greater number of tender and swollen joints, and the number of tophi. Of importance, among the 110 patients enrolled in this study, four died during the course of this one-year observational study.

The aim of urate lowering in these patients who have progressed is to prevent further deterioration and, in fact, to reverse the affliction and limitations in these individuals. Such manifestations as this cluster attack of gout in the proximal interphalangeal joints in a patient who already has destructive arthropathy, who has these whitish deposits that are tophi, that, in the course of this inflammation, threatened to break through the skin and leave draining ulcerations.

More often, urate crystals accumulate in the form of large masses of tophi, as in this individual, who is a patient of mine, with an

allergy, a severe cutaneous reaction to allopurinol, many, many kidney stones, precluding uricosuric therapy, and an inability to lower his uric acid over many years.

Or this woman, also a patient of mine, who had a misdiagnosis because she had an inflammatory polyarthritis and an elbow nodule misinterpreted as a rheumatoid nodule. She was treated for rheumatoid arthritis for many years and by the time the diagnosis of gout was made, she had significant renal impairment, precluding the use of the usual urate-lowering agents.

And, finally, this individual, who has severe impairment of the use of his hands. This is an individual, also, with an allopurinol rash problem and, in fact, who resisted allopurinol desensitization, and, ultimately, was unable to maintain his job as a graphic designer.

In summary, treatment failure gout is an unmet medical need, one that requires disease modification in a big way. People with this syndrome are a small subgroup of gout patients

with a high symptom burden, significant deficits in the quality of life and their function, and significant associated co-morbidities.

Current oral urate-lowering therapies require many months to years of treatment to reduce or reverse the signs and symptoms of gout. An agent effective in the management of treatment failure gout should deliver potent long-term urate-lowering efficacy, provide early and sustained evidence for clinical benefit, and be safe relative to the benefits likely to be achieved.

I believe that on the basis of the studies in which I participated, that pegloticase fulfills these criteria. Thank you.

I'll now introduce Dr. Vibeke Strand from Stanford to present information on the efficacy in the pegloticase program.

DR. STRAND: Dr. Becker and Dr. O'Neil, members of the panel, FDA and the audience, I am pleased to present the efficacy of pegloticase for the treatment of treatment failure gout, Phase 2

and Phase 3 studies. Phase 2 was a multicenter three-month study that was open label in 41 patients, where various doses of pegloticase were studied, and it was shown that doses of equal to or above 8 milligrams were effective in maintaining uric acid levels below 6 milligrams per deciliter.

The Phase 3 studies are replicate multi-center, randomized, double-blind studies, C0405 and C0406, of 104 and 108 patients, conducted in the U.S. and Canada and the U.S. and Mexico. They were six months duration, they were blinded, and two doses of pegloticase, 8 milligrams every two weeks and 8 milligrams every four weeks, were compared with placebo.

A multi-center open-label extension 0407, subjects who completed the two Phase 3 studies were allowed to choose either every two-week or every four-week treatment regimen without knowledge of their assignment in the randomized trials. And finally, a small 0409 study allowed re-exposure in subjects who had not received

pegloticase for a prolonged period of time.

The design of the Phase 2 study, as I mentioned to you, was multi-center, but open label. It was designed to understand the preliminary efficacy and safety of pegloticase and the pharmacokinetics. Four and 8 milligrams were administered either every two weeks or 8 and 12 milligrams every four weeks.

The results indicated a very rapid and sustained normalization of plasma uric acid levels at doses equal to or above 8 milligrams, thus, the two doses that were selected for Phase 3. Anti-pegloticase antibodies were observed, which resulted in enhanced clearance with high-titer antibodies. These were IgM and IgG, directed against pegloticase, and they were non-neutralizing.

Observed in this Phase 2 study is a pattern that we saw in Phase 3, as well. Looking at the eight patients who were treated at the 8 milligram every two-week regimen, you can see that there are six persistent subjects who have

persistent responses, immediate and rapid lowering of plasma uric acid levels that are maintained low throughout the treatment time, whereas there are here two transient responders, again, with very rapid lowering of plasma uric acid levels, but subsequent loss of effect between weeks two, four and six.

The Phase 3 program, as I mentioned to you, was six months duration and blinded. The randomization was 2:2:1 for treatment to placebo. These are the numbers of subjects who were randomized. As you can see here, 43-42 and, again, 20 and 23 for the placebo group. After completion of the Phase 3 studies, subjects were enrolled in open label, and some did, a few, two, two in that number chose to be in observation as opposed to treatment.

The major inclusion criteria for the study was that allopurinol had been either contraindicated or ineffective at the maximum medically appropriate dose for at least three months; that the serum uric acid was 8 milligrams

or above; and, that the subjects had symptomatic gout with at least one of the following: more than or equal to three flares in the past 18 months, by their report; at least one tophus; or, the presence of chronic gouty arthropathy.

The major exclusion criteria were cardiovascular disease, defined as unstable angina, uncompensated congestive heart failure, poorly controlled arrhythmias or uncontrolled hypertension, in this protocol, defined as greater than 150 or over 95.

Dialysis was an exclusion criteria, although there was one subject who was enrolled who was receiving dialysis. History of solid organ transplantation was an exclusion, as was G6PD deficiency, because of the warning contained in the rasburicase label.

A pre-specified fluoroprophylaxis included colchicine or analgesic doses of non-steroidals with a PPI or no subjects intolerant of the above two, they could receive glucocorticoids in doses equivalent to 0.5 to 1

milligram per kilogram of prednisone.

Based on the Phase 2 study, there was a pre-specified infusion reaction prophylaxis, which included a non-sedating antihistamine, fexofenadine, the night before, fexofenadine and acetaminophen the morning of the infusion, and 200 milligrams of hydrocortisone IV immediately prior to the infusion.

The valuation schedule is, as you can see here, plasma uric acid and serum uric acid determinations were performed at every visit. Subjects received either active or placebo dosing every two weeks. In the q4-week group, that would mean that they received placebo on alternate visits. The secondary endpoints were assessed at weeks 1, 13, 19 and 25.

The primary endpoint was a plasma uric acid, which was based on intensive sampling during month three and month six, whereas one can see here there are trough levels assessed at each visit, but, also, two and 24-hours after an infusion, there's pharmacokinetic assays to look

for peak plasma levels of pegloticase.

As was shown in these patients, the relationship between serum uric acid and plasma uric acid was very close, with discordance in 4 percent and 1 percent. Plasma uric acid was determined to be the appropriate outcome because of the concern that pegloticase could, in fact, alter, enzymatically alter the uric acid levels. Thus, these samples were iced and acidified and precipitated for handling.

The definition for the primary analysis was a value of plasma uric acid less than 6 for greater than or equal to 80 percent of the sampling period during the intensive sampling times in months three and six, as shown to you.

A responder analysis meant that there were no data imputed. Persistent responders were defined as I showed you for Phase 2, meaning that those were subjects who maintained a plasma uric acid response throughout versus transient responders, which were those who lost a response between weeks 2 to 6 to 10.

The statistical analysis plan included the intent to treat population and either active treatment was compared with placebo. The secondary endpoints -- it was agreed with FDA that an a priori pooled analysis of treatment groups across studies would be made. There were no adjustments for multiple comparisons. LOCF was performed where specified.

In terms of the subject disposition, in fact, almost 6,000 contacts were made related to advertising, of which 1,500 were referred for detailed screening, which resulted in 65 subjects who were found to be eligible for the study. Principal investigators identified 160 subjects; thus, 225 were randomized. We can see here that 85 were dosed in the pegloticase q2-week group, 84 in the q4-week group, and 43 in the placebo group.

Sixty-nine and 70 percent completed in the active treatment groups and 91 percent in the placebo. Baseline demographics were relatively similar between the two studies. You can see that they were predominantly male and Caucasian and

that the mean BMI was elevated in both groups.

There were some baseline disease characteristics that were different. All of them, of course, were either allopurinol ineffective or contraindicated. Differences in the percentage of subjects with tophi present, although randomized equally within the protocols, those who reported crippling flares, the mean flares per year reported by the subjects, and the tender joints.

The HAQ Disability Index, a measure of physical function, does show some variability between the treatment groups with a low of .87 to a high of 1.66 in the two different placebo groups in the two trials.

Medical conditions at baseline were as might be expected in a treatment failure gout population, 85 to 81 percent of subjects had cardiovascular conditions or risk factors at baseline, which included coronary artery disease, congestive heart failure, et cetera. Thirty percent of them had impaired renal function. Obesity was present, sleep apnea, and other

co-morbidities.

The primary endpoints were the percentage of subjects with a prolonged and persistent plasma uric acid response. As one can see here, that was in 47 percent and 38 percent of the pegloticase q2-week treatment group, which was high statistically significant. Statistical benefit was also present in the pegloticase q4-week group.

Now, if we look at the mean plasma uric acid in all the subjects in the combined Phase 3 studies, we can see that there was absolutely no change in the placebo group and there was a rapid and sustained response in the pegloticase q2-week group and there was a rapid response in the pegloticase q4-week group, where the means then were roughly equal to 6 milligrams per deciliter plasma uric acid.

If we now divide this group into the persistent responders, of which we have 36 persistent responders in the pegloticase q2-week group, we can see that the plasma uric acid level is rapidly lowered and is sustained at very low

levels. In the pegloticase q4-week group, in the sustained responders, we see benefit, as well, and this was a number of 28.

In the transient responders, one can see placebo, again, the pegloticase q2-week group, where there is a rapid response, but it is subsequently lost between weeks three and 12, and the pegloticase q4-week group, where one can see the same thing. The transient responders in the pegloticase q2-week group were a total of 48.

If we look at the persistent responders who were receiving pegloticase q2-week and then entered open label treatment, 21 of them went into pegloticase q2-week treatment and 14 of them entered pegloticase q4-week treatment. Two subjects discontinued here, resulting in 19 that could be observed, and there was a loss of response in there of these subjects. One subject discontinued here, and there was a loss of response in three subjects.

So conclusion from the plasma uric acid data, the primary endpoint was met in replicate

trials, indicating that normalization of plasma uric acid to a level of 6 milligrams or less during months three and six was achieved. These were dramatic and durable reductions in persistent responders.

Subjects who switched from placebo in the RCTs to pegloticase q2-weeks in open label demonstrated similar responses, although the data I did not show.

The transient responders can clearly be identified by routine serum uric acid monitoring, usually within the first three months of therapy. And finally, in those receiving q2-weeks treatment, the majority of persistent responders maintained those responses through week 53.

The secondary outcome measurements included a complete tophus response, gout flares, physician reported outcomes, and patient reported outcomes, which included global assessment of disease activity and pain by a visual analog scale, physical function by the HAQ Disability Index, and health-related quality of life by the

SF-36.

The definition of a complete tophus response was either a 100 percent decrease in the area of a precisely measured tophus or disappearance of globally measured tophus and no development of new tophi or progression in any other tophi. Photographs were taken by the investigators and independently adjudicated by Dr. Robert Pineals and one other rheumatologist.

I can show you an example of what this looks like. So this is one subject at baseline. This would be considered to be a globally measured tophus that can be a maximum of 10 millimeters in diameter or the precisely measured tophus, which can be precisely measured in two different ways and was approximately 5 millimeters in diameter.

This is now the week 13, where you can see that there's already some change in both the precisely and the globally measured tophus; week 19, where there's further resolution. And I point out to you that there were other tophi that were not included in the measurement that are now also

improving; and, finally, the week 25 results, where there is marked clinical improvement in these disfiguring tophaceous deposits on this subject.

The tophus response was pre-specified in the pooled analysis and was present in 40 percent of subjects receiving pegloticase q2-weeks, representing 21 of the 52 subjects who had tophi at baseline. This was not statistically significant in the pegloticase q4-week group and two patients in placebo ostensibly had tophus responses. In fact, the resolution in the persistent responders was already evident at week 13, as I showed you, and was present in 17 of 21 at the final visit.

So pegloticase q2-weeks treatment results and complete tophus responses, and these responses are observed even at the first assessment, at week 13, and this does represent the pharmacodynamic effect of pegloticase, indicating that there is a strong evidence of reduction in total body urate pool.

The secondary endpoint was a reduction of gout flares through months four through six based on the expected increase in flares months one through three, after initiation of urate-lowering therapy. Thus, the incidence and frequency of flares months four through six were assessed as an efficacy versus placebo. Subject-reported flares were confirmed by investigators and one can see here that the number of flares in the active treatment groups were higher than placebo in months one through three, but statistically less than placebo in the pegloticase q2-week group versus placebo in the second four to six months.

Pre-specified pooled analysis indicated the statistical significance that I just showed you, and the frequency of gout flares in the persistent responders were higher during the randomized controlled trial, but in open label, in fact, were lower than those in the transient responders, and note, of course, that there are fewer flares over time as subjects continued pegloticase treatment.

Tender joint count was statistically significant in the pegloticase q2-week group, as well as pegloticase q4-week group. Note that this is ostensibly a mono-arthropathy and, in fact, we're seeing here that they have tender joint counts of 12 to 14 joints. The physician global assessment also indicated significant disease activity at baseline of 47 to 52 on a 100 millimeter VAS scale, with significant improvements in both treatment groups.

Patient-reported outcomes included the global assessment of disease activity, the pain VAS scale, physical function, and SF-36. You can see here the global assessment was very similar to what the physicians had assessed, significant disease at baseline and statistically significant improvement in both pooled treatment groups, pegloticase q2 and q4-weeks.

One can see here, over time, that there is progressive improvement in both treatment groups and there is, in fact, deterioration in placebo at weeks 19 and 25. Understanding that

the minimum clinically important difference, that amount of improvement that's perceptible to patients is considered to be 10 points on a VAS scale and we can see here that at endpoint, 54 percent of the subjects receiving pegloticase q2-weeks reported improvements that met or exceeded MCID.

In the open label, we can see that these benefits were further increased or sustained. Patient-reported pain also indicated a significant level of pain at baseline, which was statistically improved, and this mean was greater than the MCID in the pegloticase q2-week group. We see a similar pattern during the randomized controlled trials, better improvement in the q2-week group, and, in fact, deterioration with placebo over time. And, again, 55 percent of subjects reported improvements that met or exceeded MCID and that these improvements were sustained or further increased with open label treatment.

The health assessment questionnaire indicated that there was a fair amount of

impairment in physical function at baseline between 1.1 and 1.24 and improvements which met or exceeded MCID as means in both active treatment groups. A similar pattern is shown, in fact, where placebo actually reports deterioration at all time points and 45 percent of subjects reported improvements that met or exceeded MCID, with, again, sustained or further improvement in open label treatment.

Finally, if we look at the SF-36, the physical component summary score is calculated based on all eight domains, with a mean of 50 and a standard deviation of 10, and the mean of 50 is considered to be a normative score. As you can see here, these scores are low. They're one to two standard deviations below the normative values for the U.S., and the improvements are large in both treatment groups.

MCID is considered to be 2.5 to 5. Improvement points in the PCS score, you can see that the active treatment groups reported improvements that were well above that at all time

points; 64 percent in the pegloticase q2-week group reported improvements that met or exceeded MCID and at week 25, in fact, deterioration with placebo and further improvement with open label treatment. But the PCS score doesn't really show the full dimensions of the effect of treatment failure gout on health-related quality of life. And if we look across all eight domains, we get a better picture of what this is.

So physical function, low physical pain and general health are the four physical domains from 12:00 to 5:00; vitality, which is also fatigue, social function, low emotion or mental health are the four mental domains. The scores on the domains go from zero to 100, with the best scores being 90 to 100, and these are 10-point degradations here to indicate that MCID is an improvement of 5 to 10 points.

If we now look at the baseline scores in the pegloticase combined treatment group and compare it to their age and gender match norms, which are specific to this protocol population,

one can see the effect of treatment failure gout on health-related quality of life. It's quite dramatic, not just in the physical domains, but also in fatigue, social function, and low emotional.

If we then look at the improvement in the placebo group, we can see that very little changed over the time of treatment and six months in the protocol. And if we now compare this to the improvement in the pegloticase q2-weeks treatment group over six months, one can see, first of all, that improvements in all eight domains met or exceeded MCID and, in fact, they now meet or approach age and gender match, normative values, in four of the domains. These were statistically significant in six domains and they were all clinically meaningful in terms of being changes that met or exceeded MCID.

The dose regimen was selected to be pegloticase q2-weeks based on the fact that there were more persistent responders, more subjects would complete tophus responses, there were better

physician-reported measures in this treatment group that are patient-reported outcomes, fewer flares amongst four to six and continuing in open label, and fewer infusion reactions, which will be discussed by Dr. Schweiterman.

If one looks at a number needed to treat analysis on based improvements reported by patients, in other words, the number of subjects that need to be treated to obtain one good outcome as opposed to an NNH number needed to harm, we looked at the persistent responders in the pegloticase q2-week group, of which there are 36. We can see that actually 31 of them reported improvements that met or exceeded MCID in one of these four parameters and 23, 15 and 8 in two, three or four, all four parameters. This resulted in number needed to treat numbers, which were exceedingly low, 1.2 to 4.5, to make a clinical difference in what patients would report as being important to them.

So in summary, pegloticase 8 milligrams every two weeks results in significant decreases

in plasma uric acid values, which are durable in those subjects who are identified to be persistent responders. These data are actually the first demonstration of clinically meaningful and statistically significant improvements in signs and symptoms of gout in randomized controlled trials, and these improvements really do represent disease modification in this treatment failure gout population.

Thank you very much. And I'd like to now introduce Dr. Bill Schweiterman.

DR. PACKER: Dr. O'Neil, can we take some questions here, because otherwise we're going to get efficacy questions and safety questions commingled? Do you want to do that or do you have a preference?

DR. O'NEIL: The plan was to wait until the sponsor had finished their presentation and then we can speak to each of these issues.

DR. PACKER: Okay.

DR. SCHWEITERMAN: Thank you very much, Dr. Strand.

My name is Dr. William Schweiterman. I'd like to present the safety data for pegloticase.

The agenda for the safety discussion includes a discussion of adverse events, serious adverse events, including all cause mortality and gout flares. I'm going to spend some time discussing in detail the immunogenicity of pegloticase. It's an important topic for both the safety and efficacy. I'm going to put this in the context of several different parameters to try to frame the optimal benefit-risk of this therapy. Dr. William White will discuss the cardiovascular evaluation and safety following my presentation and then there will be a conclusion.

The total exposure for the clinical development plan for pegloticase was 273 subjects, ranging in doses from .5 to 2 milligram, 12 milligrams intravenous. Two hundred and eight subjects were studied in the Phase 3 program, 169 in the randomized controlled study itself, with 39 additional patients studied from the open label extension from which they came from placebo in the

randomized controlled study, comprising 151 total in the open label extension.

Notably, we collected numerous chronic safety data. This is a chronic disease. And we have 140 subjects exposed for greater than or equal to six months, 121 subjects exposed for greater or equal to 12 months, and 95 for 18 months.

This is a table showing the discontinuations in the Phase 3 study. Notably, there were approximately 30 percent discontinuations in pegloticase receiving q2 or q4, with approximately 9 percent in placebo. The chief reasons for discontinuations were infusion reactions and gout flares, these two adverse events. Other causes of discontinuations are listed below here. Notably, the deaths were balanced between the treatment arms. There was no censoring rule in place for the deaths, and they're listed here accordingly.

This is a description of all cause mortality and the deaths that occurred during the

study. Again, three deaths in pegloticase q2, one in pegloticase q4, and three in placebo.

Dr. White is going to go in detail over all the cardiovascular data. These are two cardiovascular deaths, with extensive co-morbid conditions. A patient died of decubitus, staph sepsis infection; in one case, a renal failure when he declined further treatment.

The deaths on placebo, one was -- died just after randomization, but prior to the first dose of therapy, and then two other deaths are listed here, four months after treatment discontinuation.

This is a table showing subjects with adverse events. Several important points here. Number one, 95 percent of the placebo patients themselves reported adverse events. This is a very sick patient population, 94 percent and 100 percent in the q2 and the q4 arms, respectively, showed adverse events. But discontinuation rates, about 24 percent. The number of subjects with serious adverse events is shown here, 24, 23 and

12 in the q2, q4 and placebo arms, respectively, with discontinuations around 11 to 8 percent range.

This table, again, shows the serious adverse events broken down this time by disease category. This is a table, actually, of any serious adverse event that occurred in greater or equal than equal to two pegloticase-treated subjects and greater or equal to 1 percent more frequent than placebo, infusion-related reactions. And gout flares were notable serious adverse events here.

Just a note on gout flares. They occurred in 5 percent of q2, 1 percent, and five percent of the patients on placebo, or two patients overall.

Again, this was a 2:2:1 randomization in this study.

Cardiac disorders, as I mentioned previously, will be discussed by Dr. William White. But just to summarize here, 5 percent and 4 percent in the pegloticase arms, with none in

placebo. These will be discussed in detail.

For completeness, this is a description of the treatment emergent adverse events, listed here by order of decreasing frequency in the pegloticase q2 arm, nausea, headache, contusion and nasal pharyngitis were the four most common treatment emergent adverse events that occurred greater than placebo at relatively low rates, but some were greater than placebo, and the other adverse events are listed here.

Dr. Strand mentioned that there was an increase in the -- decrease in the gout flares -- excuse me -- in the second half of the study. This is a graphic showing the study broken down into the first half, months one through three, second half of the study, months four through six.

In the first half of the study, patients receiving pegloticase tended to have higher numbers of gout flares, as is consistent with any other urate-lowering therapy. The pegloticase q2 arm is shown in aqua, P value of .16, and transient -- excuse me -- P q4 shown in the P of

.02 diagram here. At the end of the study, however, quite the opposite was true. Patients had fewer adverse events, as Dr. Strand mentioned.

This is a description of all gout flares. There were a sizeable number of gout flares experienced by all patients, 77 percent in q2, 83 percent in q4, and 81 percent in placebo. Discontinuations because of gout flares were relatively infrequent, only 5 and 2 percent in q2 and q4, respectively, and one patient on placebo. And the number of serious flares was relatively low, as well.

So in summary, gout flares were the most common treatment emergent adverse event, occurring in approximately 80 percent of the subjects. In the randomized controlled trial, there was a transient increase in their incidence and frequency of gout flares. This is consistent with other urate-lowering therapies. And in the label, we're going to provide guidance for prophylaxis on gout flares.

Finally, infusion reactions, this is this

table that shows the number of patients with infusion reactions. Again, the incidence is 26 percent in q2, 40 percent in q4, and 5 percent in placebo. The discontinuation for infusion reactions is also listed here, 11 and 13 percent, respectively, for q2 and q4. And relative few of the infusion reactions were reported as serious, although we're going to go over that in some detail.

I'd now like to present the immunogenicity data as it relates to three important topics. This includes increased clearance of pegloticase, the loss of serum uric acid, plasma uric acid response, and the increased risk of infusion reactions.

First, though, just a general overview. Eighty-nine percent of the subjects developed anti-pegloticase antibodies. These were generally low-titer antibody in many patients. Clinical manifestations were generally observed in those with higher titers, those with greater than 1:2430, which compromised about 59 percent of the

trial subjects. The antibodies recognized the PEG moiety of pegloticase and both IgM and IgG heavy gene isotypes were observed. Antibodies to uricase were rare and anti-IgE pegloticase antibodies were also infrequent.

First, again, on the increased clearance of pegloticase, this is a graphic showing the PK data for pegloticase for patients who are persistent responders. On the X axis is time and study week. On the Y axis is mean serum pegloticase concentrations.

What you see here is that patients have an initial peak of pegloticase that then achieves a steady-state. The gray areas here are the times, as Dr. Strand mentioned, of intense PK sampling to determine peaks, the peaks being about two to three above the trough levels.

This is consistent in month three through month six. Again, these are for transient responders -- for persistent responders -- excuse me. For the transient responders, shown in yellow here, there was a far different pattern of

pegloticase PK. They had the initial peak at the first dose, as might be expected, but very quickly achieved a steady-state trough level that approached zero throughout the remainder of the study; rapid clearance of pegloticase in those who had lost their serum uric acid control versus those who were persistent responders.

If you take these same data, this is a PK slide, again, comparing it with immunogenicity, this time using area under the curve, dividing it into weeks 1 through 3 and weeks 9 through 13, weeks 2 through 25. Again, these are persistent responders, those patients who had control of their serum uric acid.

They had an initial low AUC and then increased and maintained that increase. And their antibody levels were generally relatively low. This is mean antibody titer here shown on the logarithmic scale, going from 10 up to 100,000. Patients who were persistent responders had initially mean levels of antibody at 105, increasing to approximately 662, 676 throughout

the remainder of the study.

When you look at the patients who were transient responders, those patients who did not maintain a serum uric acid level of less than six milligrams per deciliter, they have an AUC that is low and then continues to get lower, to near zero, through the end of the study. And as you might expect, these patients have a much different antibody profile.

Again, mean antibody titer for these patients is shown on the Y axis. The patients presented with at least 1:2735, well above the cutoff that we defined initially as meaningful, and they increased in order of magnitude up to 1:38000 and 1:47000 by the end of the study, clearly, an association with immunogenicity and loss of pegloticase in the in the serum.

I'm now going to tie this together as to how it relates to serum uric acid and plasma uric acid response. These, again, are the persistent responders, the patients that we intend to treat with pegloticase. They have initially high

levels, dramatic drops in the serum uric acid that maintain low levels of serum uric acid throughout the study. The mean serum uric acid, again, is shown on the Y axis.

When you look at the antibody titer, again, on a logarithmic scale, these patients have relatively low levels of antibody, 1:100, well below the 1:1000 through the remainder of the study, which is quite a contrast from the patients who are transient responders, who have an initially high level of serum uric acid that drops after initial therapy.

But the mean levels of these antibody titers then increased throughout the remainder of the study, and, again, these patients have high mean levels of antibody titers. So antibody generation during the study is clearly related to pegloticase serum concentrations, which then relates to their control of serum uric acid.

It's important to note, however, that while there is a very tight correlation with immunogenicity overall in the study, that patients

developed antibodies to this agent, and if they develop high titers, they're transient responders at some point during the study. That's not necessarily a one-to-one correlation temporally. That is, the timing of the loss of serum uric acid response is not coincident with the timing of the rising antibody titers.

I'm going to show that to you here in a build slide. This is, first, the patients who had lost their serum uric acid response during the study. All individual patients are noted with yellow dots here. Study week is shown on the X axis. Again, these are all, by definition above 6 milligrams per deciliter.

Notice that most of these patients lost their serum uric acid response early in the study. Week three and week five, for example, a large fraction of the patients lost them and, certainly, by week 17 and week 21, all the patients had lost their serum uric acid response.

When you correlate that directly with the antibody titers that exist for these patients,

again, this is the same patients, each represented here by a yellow square, weeks is on the X axis, antibody titers is on the Y axis.

You see, for example, at week three, that there's a wide variability in the antibody titers for each of these patients. Even though they had lost their serum uric acid response, their individual titers varied from less than 1:100 to greater than 1:100000.

Antibody titers themselves are not predictive, not coincident with the rise of serum uric acid. Rather, serum uric acid itself is a better predictor of immunogenicity than the antibodies.

So in summary, the loss of serum uric acid response indicates the development of anti-pegloticase antibodies and to pegloticase. Antibodies lead to increased drug clearance, a decrease in uric degradation, and measurement of SUA is an effective indicator of the presence of active pegloticase and clinically important anti-pegloticase antibodies.

I'd now like to show how immunogenicity relates to increased infusion reactions. This, again, is a slide I showed before. Just to recap the incidences, it was about 26 and 40 percent in q2. Discontinuation for these patients was about 11 and 3, and about 5 and 8 percent in the q2 and q4 arms were labeled as serious.

After the company received these, we performed a very intensive review of all the patients who had experienced an infusion reaction, whether they were reported as serious or not, whether they were reported as severe or not, and looked very carefully at their signs and symptoms, and I'm presenting here the results of this. This is actually a review of the patients in the randomized control trial and it's infusion reactions that had features of hypersensitivity.

Included in this analysis is any patient that is stridor, wheezing, peri-oral/lingual edema, hemodynamic instability. Eleven such subjects out of the 56 were identified. Five have already reported as SAEs. Six out of the 11 were

not reported to the SAEs, despite having these symptoms, and 10 of the 11 were discontinued. All were managed with supportive care, as shown on this slide, antihistamines, acetaminophen, glucocorticoids, slowing and stopping of the infusion and restarting it at a slower rate was often helpful for these patients.

The outcomes themselves showed that all of them recovered and, result, fine, there were no hospitalizations. There was some mechanical ventilation. One patient received epinephrine. And notably, as I mentioned before, because we're looking very carefully at serum uric acid, nine of the 11 subjects experienced an infusion reactions after they had actually lost their serum uric acid response. Two of them did not. Two of them occurred on the first dose and these patients were very carefully examined. Neither one was hospitalized. Neither one of them had high baseline antibody titers.

This is just a very brief review. You're going to hear fully from the FDA following my

presentation and the company's presentation. So I'm not going to go into this, except just to say, from our point of view, the FDA identified, also, patients who had signs and symptoms suggestive of hypersensitivity response. They used the FAA and Symposia criteria, another definition of anaphylaxis. There's no clear definition available in the literature.

I want to point out that five of their -- they had studied a slightly different database, five were in the randomized controlled study. We identified all these cases, as well as other seven potential cases. The definitions will be gone into by the FDA reviewer, but include, again, the signs and symptoms of stridor, wheezing and so forth in various combinations.

This is a very busy slide, but I'm going to make two points about this. After receiving the FDA review and looking at our review, we compiled actually all the patients who had any sign and symptom suggestive of anaphylaxis and put it on one slide.

So the first point I want to make is that these are not all cases of anaphylaxis or even necessarily of severe hypersensitivity, but rather the complete compilation of all the patients with regard to their patient number. We identified which ones were identified by us and them, again, somewhat different datasets that we used, what study they were in, when they experienced the dose and so forth.

So this is a wide variety of patients with signs and symptoms of anaphylaxis of any sort. We actually identified some that weren't identified by the FDA, if they had even some transient systems and so forth, and looked very carefully at the immunologic profile of these patients, which we can discuss further in the Q-and-A, if you'd like, to discuss the kind of analysis we did.

What's important to note is the variety was there and the correlations weren't there, and this represents the universe of patients we had. But perhaps the most important point is that of

all these patients that we compiled, all but two would have been able to have been prevented had they not received their pegloticase further, having lost their serum uric acid response.

So you see a column here on serum uric acid. All these numbers down the row here shown in yellow show that it's greater than six milligrams per deciliter. And, as I'm going to show, in several slides, we believe this is a very important risk mitigation strategy for these patients, since infusion reactions occur in those who develop immunogenicity and, more specifically, occur in those who actually have lost their serum uric acid response.

The two patients that would not have been prevented by this are shown in yellow. I'm not going to go into detail, but these are the very two patients I mentioned earlier who had lost their serum uric acid -- who had had their infusion reaction before loss of serum uric acid response, these on the first dose. Again, both were managed as outpatients.

These are similar data that I showed previously on loss of serum uric acid response, this time very specifically going with the dose that we're proposing. There was a slightly more increased risk of infusion reactions in the q4 arm and, as importantly, of the subjects who received pegloticase q2, 20 of them experienced their infusion reactions after loss of serum uric acid. One did not, and, again, we're talking about the same patients here.

One of the patients who received pegloticase q2 at the randomized controlled trial had their infusion reaction at the first dose. Overall, of the 273 subjects that had any type of infusion reactions, they were only two that were deemed anaphylactic, less than 1 percent in our study.

So the summary of infusion reactions is as follows: 49 of the 56 subjects, 88 percent, had infusion reactions after their SUA was greater than 6 mgs per deciliter. In the pegloticase q2 arm, I'd just show you these data, greater than 91

percent had IRs after the loss of serum uric acid response. Anaphylaxis, nine of the 11 had theirs after loss of response, and the loss of response tended to occur early, within three months in all patients.

For these reasons, and I'm going to present a risk mitigation strategy after the presentation by Dr. White, but we are going to propose very specific guidance in the label for use of pegloticase. In particular, patients should receive medical prophylaxis prior to infusion. Some of the patients in that list had not. That includes antihistamines, acetaminophen, glucocorticoids.

We're also going to strongly recommend that patients discontinue pegloticase when they've lost their serum uric acid response. This, of course, is to reduce the need for needless exposure. They're not likely to have the benefits of therapy, but as importantly, they're also likely to perhaps experience infusion reactions if they had; and the converse is also true. If they

have a loss of serum uric acid response, they tend not to experience those.

And then, finally, if any patient discontinues -- if any patient experiences an infusion reaction of moderate to severe severity, they should also discontinue therapy. We believe that this is a very powerful predictor of the likely safety and efficacy of pegloticase and allows for a very effective risk mitigation strategy for these patients.

I'll now turn the podium over to Dr. White, who will discuss cardiovascular SAEs.

DR. WHITE: Good morning, everyone. I'm Dr. William White from the University of Connecticut School of Medicine in Farmington. I actually served as chair of an independent adjudication committee looking at severe cardiovascular events and all that's in the pegloticase case program.

I'm going to review some of the nonclinical and mechanistic findings before I get into this evaluation project that we did. I will

review with you some other information on the burden of disease within this population and the effects of the drug on cardiovascular risk factors, including things like blood pressure and cholesterol and so forth, and then, also, tell you a little bit about our methodology for the adjudication process, followed by the summary of the results of the cardiovascular evaluation.

So there have been some mechanistic studies, as well as some animal studies done with pegloticase that are relevant to cardiovascular morbidity. There has been a 39-week canine study with exposure to the drug, in which vital signs, QT intervals, morbidity was evaluated. In fact, there were no changes in morbidity, mortality, and at sacrifice, the myocardiums of these animals were normal, as were their coronary arteries.

Now, there has also been an evaluation of hydrogen peroxide degradation, the rate of hydrogen peroxide degradation by red cells vastly exceeds hydrogen peroxide generation by pegloticase therapy.

There has been some interesting work done at Duke recently that maintaining a plasma urate at less than 2 with pegloticase up to three and a half months does not raise the plasma isoprostanes, a validated biomarker of oxidative stress, and there has been a formal post hoc blinded QTc evaluation in all the electrocardiograms done in the program, which showed no changes relative to placebo.

So as you've already heard from other speakers, the population has a fairly high cardiovascular risk burden, with over 80 percent having disease or risk factors, many of them multiple and scattered among a cluster of things, including a high proportion of hypertension, dyslipidemia and diabetes, which is rampant in this particular treatment failure gout population, and a fairly high percentage of patients with actual vascular disease, more than 25 percent having either stroke or coronary disease history and a fairly high proportion of heart failure and arrhythmias.

So in evaluating the risk factors analysis, this is a summary slide of looking at this, the changes according to q2-week, q4-week administration or placebo. Systolic blood pressure, in fact, did not rise in the population and was not different among the three treatment groups.

The plasma glucoses did go up in all three treatment groups. This was due, in fact, to a couple of outliers in each of the groups who lost control at some point in time during the study. Total cholesterols were not different among the three treatment groups, and body mass index went up by less than half a kilo in the q4-week group and .1 and .1 in the q2 and placebo group, respectively.

Because there's been some great interest in blood pressure as a cardiovascular risk factor, I just want to show you an outlier analysis we performed on systolic blood pressure in the three treatment groups. This light blue is q2-week and the yellow is q4 and the darker purple is placebo.

This goes from changes that were lower by 10 to 20 on this end of the graph and increases by 10 to 20 on the right-hand portion of the figure. So I think it's pretty obvious that there's no differences between the three treatment groups for increases in blood pressure nor were there differences for decreases in blood pressure on either extreme end of the spectrum of systolic blood pressure in the population.

So getting to the methods of our committee, we were asked to perform an independent post hoc review of potential cardiovascular events identified by the MedDRA dictionary of serious adverse events. I want to point out that serious adverse events had narratives and other supporting documentation. Non-serious adverse events in this program had the typical stating of the event, without documentation or narratives or other information that would have allowed for a proper adjudication process.

Now, the committee was naive to this whole program at the time we were asked to

participate and were certainly blinded at treatment group assignments and had no knowledge of trial result. The committee members were also not initially looking at serious infusion reactions, because there were concerns that that would, in fact, unblind the group. That was done later by myself.

The committee developed a charter to develop the processes and the various endpoints and included myself, a cardiovascular expert at Ohio State, Glen Cooke, and Phil Gorelick, who is a stroke neurologist at University of Illinois.

So we used, for one portion of the event classification, the Anti-Platelet Trialists Collaborative endpoints, which are also now known in many divisions as the MACE endpoints, or major adverse cardiovascular events, and we also had a clustering, which I'll show you in a moment, of non-APTC cardiovascular events, which are possible to adjudicate in such programs. Both of these classifications have been used in prior work looking at cardiovascular adjudication in both

cardiac and non-cardiac drug development.

So the APTC events included cardiovascular deaths of any kind, including sudden MI, stroke, heart failure, et cetera, defined non-fatal MIs and strokes, and then for what we are referring to here as the non-APTC major adverse cardiovascular events, that included hospitalization for unstable angina, which could include an acute coronary syndrome. It could also include somebody who then later got a percutaneous coronary intervention, or CABG.

At any coronary revascularization that was elective and not associated with an acute unstable anginal event, transient ischemic attacks, venous and peripheral vascular thrombotic and embolic events, congestive heart failure, which was typically hospitalized or treated at a heart failure center, requiring clinical signs and intervention, including inotropes or diuretics, and arrhythmia with no evidence of ischemia, and cerebral revascularization, which was typically carotid endarterectomy.

So this is the disposition of the subjects with potential cardiovascular events from both the randomized controlled trials and the open label extension and the Phase 2 program in order to keep us unaware of treatment study and so forth. We identified 56 potential events within 46 subjects.

Following the final adjudication, six of these events in six subjects were defined as APTC events. Three of them were in the randomized controlled trials, two in the open label extension, and one in Phase 2. For the non-APTC cardiovascular events, there were 17 such events in 15 subjects, 9 in the randomized controlled trials, 8 in open label extension. And we designated 31 events in 27 subjects as non-CV and these occurred 19 in the control trial, nine in the open label extension, and three in Phase 2. Two events in two patients were not given a final diagnosis by the committee. Both of these subjects were in the randomized to placebo. One of the placebo patients, which I'll show you in a

moment, was an ill defined death post-study which had not enough information to determine if it as CV or non-CV. It was defined as multisystem organ failure. So it sounded more like non-CV, but we didn't have the documentation.

In the other case, the person was actually in placebo originally, moved over into the q4-week open label extension, had dyspnea, which is the term that I chose to adjudicate it for, and this occurred after having an infusion reaction. This resolved. We had no other data to support a CV versus non-CV diagnosis.

So this is the primary table of our process for the RCTs. We adjudicated two APTC events in the q2-week group, which were both CV deaths, one myocardial infarction in the q4-week group; no strokes and no events in the placebo group.

For the non-APTC events, there were -- and so there's no confusion here, there were three events in two subjects. So it's two total non-APTC events, if you're counting the first one,

two cases of heart failure and one arrhythmia that occurred later on, not the same admission, in one of those heart failure patients.

There were seven non-APTC events in six individuals. One of these events was a second event that occurred distant in time from an MI. So it wasn't considered a first event in that sense. These were spread around in various categories, as you can see. And there were no non-APTC events in the 43 placebo subjects.

Now, it's of interest, I know, to a lot of people to evaluate how a committee like this works compared to the reports of investigators at the sites, because everybody is always concerned that adjudication committees decrease the number of events, and I just want to show you how we compare, first, for the treatment emergent APTC events from the RCTs. And here we had actual complete concordance with that reported and that adjudicated for both q2-week and q4-weeks.

In the case of the non-APTC events, however, we actually had more events adjudicated

or diagnosed by the committee than by investigator reported by two. We had agreement with the q2-week for one of the heart failures, but we actually found another one. In the pegloticase q4-week group, we also found an additional case that was not determined by the investigators.

We had agreement with angina, we had agreement with arrhythmia, and then we found an additional case of coronary revascularization that was missed by an investigator and the venous thrombotic events and transient ischemia attacks were similar.

So that's the way those things panned out.

Now, this is a table for casting of the widest net, if you will, of MedDRA terms. Now, these were the non-serious treatment emergent cardiovascular events that were designated by the MedDRA dictionary, just to show you how things resulted in q2 versus q4; 24.7 percent versus 40.5 percent and in the placebo group, 37.2 percent. You'll see that a large number of these cases were things like edema, dizziness. There were some

patients with dyspnea and hypertension, chest pain and so forth, but none of these had narratives or had information that could allow us for further assessment as an independent blinded committee.

The infusion reactions, as you've already heard from Dr. Schweiterman, are a safety point of interest. All infusion reactions were evaluated for possible hidden cardiovascular events. There were full narratives on all the serious adverse events and some others. So 26 of them, because of the terms and the severity, were formally evaluated.

Two of the infusion reactions were temporally associated with a cardiovascular event. I'd like to describe that for a second. One of these occurred in the randomized controlled trial. This was a fellow who had known coronary disease, who, actually, within the last few months, had had a percutaneous coronary intervention, had a stent put in.

During the infusion, he developed an elevation of his systolic blood pressure of about

20 points and he had very transient chest tightness and was transferred to an emergency room. By the time he had gotten there, which was actually within a few minutes, he had total resolution of his chest pain and his ECG was entirely normal. However, he was kept for observation. He underwent a cardiac stress test and two days later, he underwent another coronary arteriogram, which demonstrated a new lesion that was big enough to angioplasty in his right contrary artery, and he was discharged.

The second patient was in the open label extension. This was an individual who had a known history of cardiomyopathy and chronic heart failure, who decided that day to not take any of his medications and came in with a little bit of shortness of breath, was given his infusion. The shortness of breath got worse.

He was transferred to the emergency room, where he was found to have mild to moderate signs of congestive heart failure. He was diarese (ph) and he was improved and got better. So these were

the two cases that I determined from within the -- embedded within the infusion reaction data.

So then the next analysis was to determine whether or not there was some relationship temporally between getting an infusion and having a CV event. So this is a listing of all the subjects who had cardiovascular events. You'll notice there are two events in a couple of the patients spread in time.

Now, the reason you're looking at a purple bar and a green bar in some cases is because the patients who were randomized to q4-weeks had every other placebo versus drug infusion q2-weeks, alternating. So I'm giving you the information related to when they got the placebo and when they got the pegloticase.

So you can see, for example, in this individual, about 35 days after placebo and about 50-ish after they got the actual drug. But there's no global feeling or evidence here that there's any relationship between when the infusion was given and when an event happened, with no

skewedness towards sooner versus later and forth. So we didn't feel there was a relationship between timing of infusion and cardiovascular events.

So I'm just going to reiterate a second, because we did an analysis of events according to cardiovascular disease at baseline. As you know, that's pretty important to determine that. So you already heard about 80 percent of the patients had at least one cardiovascular disease at baseline or a risk factor, but, actually, a lot of them had much more than that. About 40 percent had three or more and 20 percent had four or more cardiovascular diseases or risk factors.

So in evaluating those patients who had an APTC event, it turned out that they all occurred in patients with four or more cardiovascular diseases or risk factors at baseline. For the non-APTC events, it was a little bit more scattered about, but the bulk of them occurred in the q4-week group, who had three or more cardiovascular problems at baseline. These two events occurring in these patients who

were called having two problems were coronary disease patients, not just hypertension or dyslipidemia. Another analysis was done about immunogenicity. As you've already hard, high titers were defined as greater than 1:2430 and for both APTC and non-ATPC, there was no distinct clustering in one category of high antibodies or not.

Finally, these are the events we adjudicated during open label extension. Just to remind you, there were two APTC events and eight non-APTC CV events. Some of the patients were treated with a q2-week regimen, in blue, and some q4. You'll note that the denominator at the beginning starts around 80 and 67 for the patients in these two groups. By the time a year or year and a half has passed, it's about half that number. So that's why the, quote, "rate" has increased. But generally speaking, again, just like the timing since infusion, here we see no clustering. There are events occurring from about one month to about 16 months at about the same

rate during the open label extension.

So in summary, patients in the clinical program did have a high risk for cardiovascular events reflective of a population with treatment failure gout. The clinical data showed no changes in the major cardiovascular risk factors with pegloticase relative to placebo.

The APTC events were low in number, occurring in three of 169 pegloticase patients and zero of 43 placebo patients. We adjudicated all cause death and they weren't censored, as I mentioned. So I just want to point out that all cause mortality occurred in four of 169 pegloticase patients and three of 43 placebo patients. One of those deaths was in a placebo patient who was randomized, but did not receive a dose of study drug.

APTC events occurred primarily in the patients with four or more cardiovascular risk factors or diseases. In contrast, high titer antibodies were not associated with cardiovascular events and we found no increase in cardiovascular

events and we found no increase in cardiovascular event rates over time with up to 16 months of treatment in the open label extension.

Thank you very much. We'll turn to Dr. Schweiterman.

DR. SCHWEITERMAN: Thank you very much, Dr. White. I'm going to very briefly summarize the safety database, provide the outline of a risk minimization plan, and then allow Dr. Becker to come to the podium to provide an assessment of benefit-risk.

First, with regard to the summary of safety, the most common serious adverse events were infusion reactions. They occurred in greater than -- most occurred in greater than -- patients who had greater than 6 milligrams per deciliter serum uric acid. Gout flares were transiently increased in the beginning of the study consistent with other urate-lowering therapies.

Immunogenicity was observed. The high antibody titers were associated with a high tendency to lose PUA responsiveness and, as I

showed, with relationship to infusion reactions, as well. The signal for the cardiac events showed an imbalance that was independently investigated and a causal link to pegloticase was not identified.

I want to provide now, as I mentioned, the broad outlines of a risk minimization plan. We have not discussed these in any detail with the agency, but rather proposing them here and just to show you what the framework looks like.

We plan to design and initiate a registry to collect and monitor additional safety data, inclusive of cardiovascular events. Our goals are to ensure that pegloticase is used only in patients with treatment failure gout. We intend to facilitate informed benefit-risk in these patients, educate on the label; recommendations with regard to prophylaxis for infusion reactions and gout flares; and, again, educate with regard to all aspects of pegloticase, including dose schedule, routine monitoring of serum uric acid, as I mentioned, and appropriate discontinuations

of therapy if they have an elevation of serum uric acid.

The registry itself, as I mentioned, and this is the broad outline, is proposed to be 3,000 subjects, the first 3,000 subjects treated with pegloticase, to evaluate principally the respective perhaps increased risk of this potential cardiovascular toxicity using major adverse cardiovascular events as an endpoint and comparing it to historical controls.

We've evaluated a number of different kinds of designs and, in this orphan population, have weighed the pros and cons of each different design and feel that this is perhaps the optimal way of going forward to estimate this. It's going to include an independent safety data monitoring board and, again, the purpose is to collect additional safety data in the first 3,000 patients so as to assess all AEs, but principally cardiovascular events, and evaluate the effectiveness, in addition to the proposed treatment guidance we're proposing.

The patient population will be patients with treatment failure gout. The analysis will be 3,000 patients and include some comparator arm. We're in the process now of evaluating different databases. The VA national database, which contains patients with gout, up to the 150,000, is something we're looking very carefully at.

Again, we would propose that we propose a hypothesis to rule out a 50 percent increase in these major adverse cardiovascular events to a 95 percent confidence interval; that is, to design prospectively a study that allows us to start with an assumption of an assumed rate, although, of course, there are challenges associated with that, and then very carefully evaluate whether there's a potential increase in that period.

The observation will be from the first dose to two years after initiation of treatment.

Just to very quickly go through this. This is the risk minimization -- excuse me. I'm going the wrong direction. The site registration and certification will include annual education

and certification by infusion specialists. Rheumatologists and nephrologists, principally, will be the likely primary caregivers for pegloticase at specified and registered infusion centers. They will be educated with regard to the use of pegloticase in treatment failure gout, how prophylaxis is to be administered, and the treatment guidance, of course, which we believe is very important, when and how to stop therapy, how to monitor patients, to exclude patients with G6PD deficiency, and any patient with uncompensated cardiovascular disease.

Patients with uncompensated cardiovascular disease were not eligible for enrollment in the Phase 3 studies and, hence, it's important that we maintain the study only in those patients who were studied. And, of course, there will be an enhanced pharmacovigilance program, as well.

Patients will be certified and put into registry. They will also be given supplemental education materials, told how to monitor and

report adverse events. A med guide is proposed to be written in concert with the FDA and there will be patient counseling.

Then, finally, the label itself, the centerpiece of discussing the benefits and risks, will include an indication for patients with treatment failure gout, a contraindication for patients with G6PD deficiency, a warning to patients who have uncompensated cardiovascular disease that they are not to receive treatment given the absence of data in the patients, and then, of course, treatment guidance for gout flare prophylaxis, infusion reaction prophylaxis and management, and, as I mentioned earlier, monitoring of serum uric acid, SUA, and guidance for when to discontinue therapy in the event that the SUA goes above 6 milligrams per deciliter.

I'd now like to turn the podium over to Dr. Michael Becker, who will discuss the benefits-risks of therapy and conclude the presentation.

DR. BECKER: So treatment failure gout is

a serious condition and unmet medical need warranting effective and clinically demonstrable benefit in a rapid fashion. It's a progressively painful and debilitating, deforming disorder. It has a high symptom burden, with tophi, crippling arthritis, compromises of quality of life that have been demonstrated, and a high incidence of co-morbidities, especially cardiovascular adverse events.

Treatment failure gout is an unmet medical need and I believe that the potent, long-term, urate-lowering efficacy imparted by pegloticase and the particularly impressive demonstration of early and sustained benefit is unparalleled, in my experience, with urate-lowering agents.

The safety issues have been discussed. A rapid and profound urate normalization occurs with this medication, but, of course, patients don't respond to their serum uric levels. What they respond to is their clinical benefit, and this is the real strength of this agent. The complete

resolution of tophi, as you've seen in a number of patients who are persistent responders, decreased incidence of flares occurring with early clinical demonstration as opposed to agents like allopurinol and febuxostat, improvements in pain, physical and multidimensional function, and it, I think, can be said that treatment with pegloticase in the 45 percent of patients or so who respond with persistent response represents disease modification.

What has been shown with pegloticase is that it has provided the first evidence within the context of a randomized controlled clinical trial of any significant improvement in clinical outcomes in gout.

The extent and direction of improvement and secondary outcomes are all in the same positive direction and, perhaps more impressively, the patient-reported outcomes demonstrate statistically significant benefits that exceed the MCID.

So I think, again, pegloticase provides

disease-modifying effects, such as might be shown here in the hands of this patient, baseline right hand, baseline left hand, and the changes in tophi, most notably, here and here in this individual.

The risks associated with pegloticase every two week infusion in treatment failure gout are predictable and should be manageable. The increased incidence of gout flares are transient, lasting approximately one to three months, and apparently with relief in flare incidence thereafter.

Infusion reactions can be avoided by the implementation of a simple stop rule based on serum urate response. Serum urate levels should be measured at the time of the next proposed infusion, and the results applied to the clinical decision.

Exposure to transient -- intransient responders will similarly be modified by this expedient. And, finally, the cardiovascular risks are addressed with the risk minimization plan

described by Dr. Schweiterman just a few minutes ago.

In conclusion, with regard to the benefit to risk consideration, pegloticase, given 8 milligrams every two weeks by IV infusion, in treatment failure gout patients, carefully selected and monitored, results in prompt and dramatic clinical improvements and disease modification; has an acceptable safety profile in light of the benefits to these individual with regard to a debilitating and advanced disease, and provides an effective therapy in an orphan subpopulation of gout patients.

Thank you.

DR. O'NEIL: Thank you. The next section of our discussion will be for the panel to ask questions of the sponsors. I would like to call the sponsors' representatives to the podium again to prepare to answer our questions. And if people could let me know when you want to ask questions, we'll start with Dr. Weisman.

DR. WEISMAN: I've got to ask a question

to somebody. I really feel -- what do you recommend for transplant patients? These are patients that were excluded from the trials. And should they continue to be excluded or should they be included if this drug is approved under the circumstances?

And the other question I had, if you could address this, maybe you or Michael could address it, these patients in the trials received a fair amount of corticosteroids over time.

DR. SCHWEITERMAN: Right, yes.

DR. WEISMAN: About 40 milligrams every two weeks, equivalent of prednisone. Do you recommend that to continue during the entire course of management of patients with this drug?

So those are two separate questions that have a lot to do with how clinically this drug will be used.

DR. SCHWEITERMAN: Yes. I am going to let Dr. Becker comment on actually both of those questions. There are no data in the transplant patients, which, of course, is something that

would need to be discussed in detail with the agency as to how and when to get that data and the breadth of the indication that ought to be going forward and the kinds of benefits they might get.

I have to say, though, that in the absence of data, it would be very difficult for us to go forward fully with that recommendation, although we could entertain that thought, if we intend to have the indication actually restricted to only those patients who are studied in the Phase 3 program, simply because the data are there, the benefits and risks have been established there, and would conceivably go ahead with other studies, if need be, in other subpopulations.

Dr. Becker, would you care to comment on that and the glucocorticoid question?

DR. BECKER: Yes. I would agree, Dr. Weisman, with Dr. Schweiterman's comments about transplantation patients who constitute a group of patients with a similar unmet need for adequate control in many instances of gout.

I think that that needs to be undertaken in the context of a clinical trial. However, I'm optimistic because I think that this agent, as opposed to the currently used agents, which often constitute a problem in conjunction with the medications taken to suppress graft rejection, that this would be a step up in manageability.

With regard to the steroid use, which was mandated as a means to suppress infusion reactions, yes, I think there were several identifiable things, such as loss of control of blood glucose in some patients. I don't think that this considerably changed the course of the efficacy information, a single dose equivalent to 40 milligrams of prednisone once every two weeks.

DR. O'NEIL: Dr. Packer?

DR. PACKER: I just have a couple questions about how the data were corrected and analyzed. For the correction of the changes in clinical response, were patients or investigators aware of the uric acid changes during the course of measurements?

In other words, I understand there were plasma levels of uric acid that were sent, but I imagine that during the routine management, that the serum uric acids were also measured. Were investigators aware what the changes in uric acid were?

DR. SCHWEITERMAN: This study was blinded with regard to serum uric acid. It's always a concern, you're absolutely correct, Dr. Packer, in studies where such routine measurements are available, that there might be some unblinding because of that. But it was very clearly specified at the beginning of the protocol that they were not to exceed these things.

In fact, one of the reasons for the continuation of the patients in the study well after they had lost their serum uric acid control, and there were some patients who went for many months afterwards, was because of no knowledge of actually their response.

DR. PACKER: Let me just make sure I'm -- I understand that you had the central lab for the

uric acids, right?

DR. SCHWEITERMAN: Yes.

DR. PACKER: And the central lab was for plasma and serum.

DR. SCHWEITERMAN: I believe that that's the case, yes. That's correct. Dr. Maroli is going to classify the -- the plasma serum was very carefully thought out.

DR. MAROLI: The plasma was handled by a central laboratory in Canada. ICON was the core laboratory in the U.S. for the routine chemistry panels. SUA did not go back to the investigators with their clinical safety results.

DR. PACKER: No problem. I understand. But here is what I want to know. Since these are patients being managed by physicians routinely, they get chemistry profiles. The chemistry profiles have uric acid in them.

DR. SCHWEITERMAN: Routinely they do, but not in this case.

DR. PACKER: No, no, no. I want to make sure that we get this right. I understand that

the study uric acids went to a central lab and those values were not revealed to the investigators. But investigators were allowed to assess clinical -- to assess uric acid, because of routine clinical -- you didn't prohibit the investigators from measuring uric acid.

DR. SCHWEITERMAN: Let me let Dr. Strand, who was the efficacy presenter.

DR. STRAND: The serum and plasma uric acids were done as part of the protocol. As a matter of fact, there are no SMA-12s or 24s any longer and one would have to order it specifically, and the investigators were not doing that as part of the protocol. So they had no way of knowing that the serum uric acid level was.

DR. PACKER: I just wanted to make sure. You actually instructed the investigators not to measure uric acid for clinical purposes during the course of the study.

DR. STRAND: That's correct.

DR. PACKER: Okay. One more follow-up question.

The data that we have on mortality and serious adverse events, are they events that occurred within 30 days or so, the usual 30-day window, or were they -- to what degree did you follow patients for death or for serious AEs for the entire six months?

DR. SCHWEITERMAN: I'm going to let Dr. White, who adjudicated all the deaths and SAEs.

DR. WHITE: A priori, Milton, there was a decision made to not sensor deaths. So they could have been found outside of the 30-day window and occluded. So there were three such deaths that occurred out of the 30-day window, one in the pegloticase patients and two in placebo. For the other events, they were basically truncated within 30 days of conclusion of the study, like MIs and anginas and so forth.

DR. PACKER: Right. So I just want to make sure I understand. The deaths are complete.

DR. WHITE: Yes.

DR. PACKER: But the SAEs are truncated

30 days after discontinuation of the drug.

DR. WHITE: That was what was occurring.

DR. PACKER: And for what percentage we have about -- I'm trying to figure this out. About 15-20 percent of patients -- what I want to know is how many patients do we not have complete uncensored data of six months for SAEs? You see what I'm asking?

DR. WHITE: Yes. I think we might have to come back and get that exact number for you, because I don't have that at the tip of my tongue, if it's okay with you.

DR. PACKER: Right, no, and that's fine. But I just want to make sure that the whole idea is in order to do true intention to treat, you have to have six month data in all randomized patients.

The conventional approach is to get SAE for 30 days after discontinuation, which is fine if the discontinuation is after the six-month period. But if the discontinuation is three months into the trial, then you won't have SAE

data for the last two months of the trial.

DR. WHITE: I'll clarify that. Okay?

DR. PACKER: And one other question, Billy, while you're there.

Why did you -- I know APTC is really popular, but generally speaking, the reason people are excited about APTC is because it is supposed to reveal either a thrombotic predisposition or it's -- I mean, it's been used in hypertension trials. But here, you don't have a mechanism.

DR. WHITE: Right.

DR. PACKER: And in the past, APTC could include unstable angina, TIA. Some people include heart failure, though I never understood why. Some people included venous thromboembolic phenomena.

Was there some concept as to why you thought APTC was the way to go, because it seems somewhat arbitrary in this case?

DR. WHITE: From a mechanistic standpoint, I agree with you entirely, because we did not identify a mechanistic reason why

pegloticase would enhance thrombosis or cause any kind of toxicity or myocardium based on the dog model, et cetera.

However, the events are obviously quite easy to adjudicate with predefined criteria, much easier than some of the other things we talk about like heart failure and arrhythmias. Therefore, we used it because it -- there's sort of a frame of reference out there for other drugs with those APTC composites, as well. So you can kind of understand if there's a 4 percent annualized rate, how does that compare to some other drug or other population with the same kind of predefined endpoints.

DR. PACKER: The major reason I bring it up is there is no right or wrong answer, but if the sponsor is proposing a risk minimization plan that focuses on MACE, one wonders why. I don't know. You understand why I'm saying this.

DR. WHITE: Yes.

DR. PACKER: The risk minimization plan ought to pursue, quote, "a signal," but I don't

know where the signal is coming from.

DR. WHITE: The other reason we looked at all the other kinds of events is because I thought that was so superior to just using MedDRA terms, because they can be exceedingly misleading in these kind of analyses, as you know. And as clinicians, we think of things like atrial fibrillation and ventricular tachycardia and so forth as an event we can kind of understand the clinical meaning for. That's why we did the other cluster as an adjudication process.

DR. O'NEIL: The next question is from Dr. Furberg, please.

DR. FURBERG: I have one comment and one question.

You're seeking approval for the drug for lifelong treatment, but you have very, very limited long-term data, safety data, and I worry about that.

You really only have six-month data, good data, and a little bit of open label information. So that's my comment.

My question relates more to maintenance treatment. I'm impressed by the acute data, the six-month efficacy data, with resolution of urate deposits and so on. But after all the tophi are gone and you remove the deposits, do you still need to give the same dose, 8 milligrams every two weeks? In my view, the maintenance dose could possibly be lower. Either you give a smaller dose or you give injections every two weeks. And I think this is an issue and it's both clinical and, also, relates to cost effectiveness of long-term therapy.

DR. SCHWEITERMAN: We agree with you very much, Dr. Furberg, that this is an important question. Slide up, please. We've actually thought a great deal about optimal treatment duration. We are not actually going to propose treatment for life with this particular agent, for two reasons. We have data from the six-month study out to the open label extension supporting about out to 18 months or so.

To be quite honest, the optimal treatment

duration with pegloticase has yet not been established, for the very reasons you point out, which we point out, however, that in six-month trials, we have reductions of plasma serum acid, resolution of the tophi and so forth, and the 120-day safety update shows continuation of these benefits. Slide down, please.

So we are going to, of course, discuss this extensively with the agency, but our recommendation at this point would be for there to be a 12-month recommendation for year-long therapy, of course, guided by both the physician and the patient, dependent upon the response of the patients to therapy, a resolution of the symptoms and so forth, and then maintenance therapy again, with some other agent that might be brought forward.

Dr. Strand, I don't know if you want to comment on the maintenance therapy. I see you have another question.

DR. FURBERG: Did I hear you to say that you're seeing approval for 12-month use initially?

DR. STRAND: Well, I think there's some points to be made here, and, that is, that 71 percent of the intent to treat population actually entered the open label and were followed for an additional 12 over the six months.

Now, overall, that represented 60 percent of the active treatment group and quite a few of the placebo, and we can show, if you want to see the detailed data, that not only is there maintained responses, but there's further resolution of tophi and patients continue to have improvement in the other parameters that I showed you.

By that definition, if you look at the folks who had received pegloticase q2-weeks, who then went to q4-weeks in the open label extension, their responses continued. But overall, the responses in the q4-week group were not as good in the first six months and they were not as well maintained in open label, whether they received PK2 or PK4.

I can give you the data, if you're

interested, but it seems to me, in the interest of time, you'd prefer not to see it.

DR. O'NEIL: The next question is from Dr. Neogi.

DR. NEOGI: I have a question about the risk minimization plan, with monitoring of the serum uric acid.

DR. SCHWEITERMAN: Yes.

DR. NEOGI: In your sponsor-provided information, there was a paragraph about the difficulty measuring serum uric acid in the presence of pegloticase and the special handling that's required, and I imagine that's what happened in the central laboratory.

How will this affect the measurement of serum uric acid in clinical practice, where that special handling procedure is not in place? And the concern really is that the monitoring of serum uric acid to identify persons at risk for infusion reactions or loss of efficacy may be missed because the serum uric acid may be falsely low.

DR. SCHWEITERMAN: It's a very important

question. We use serum pegloticase in the clinical studies as measured by plasma uric acid because of the issues that Dr. Strand mentioned.

In fact, when we look -- slide up, please. It was shown in her slides. There was a very tight correlation between serum uric acid and plasma uric acid. Slide down.

Just to put this into perspective, there was a 95 percent correlation between SUA and PUA. Four subjects did not actually correlate, some in one direction, some in the other, all borderline, with one crossing above or below the threshold. And when you look at the intent to treat analyses using either type of analysis, both showed statistical significance.

So the data clearly support use of serum uric acid, even though we used a specialized PUA in this study.

DR. NEOGI: I understand the trial data or the study data, but my concern is the -- as far as I understood from reading the sponsor-related material, that there was special handling for

measurement of serum uric acid, which may not be the case in clinical practice.

DR. STRAND: No, that actually isn't true. The plasma uric acid was specially handled. The serum uric acid was obtained by the central lab, along with all the other determinations. And so it was not specifically separately handled.

DR. O'NEIL: Dr. Mikuls is next.

DR. SCHWEITERMAN: Just one additional point here, that when pegloticase actually is in the serum and the uric acid is down, the serum uric acid itself becomes a more reliable predictor of response.

DR. MIKULS: My first question is going back to the case definition, if you will, the treatment failure gout population. I'm interested what proportion of those patients had a dose limiting co-morbidity? And what I'm specifically asking, how many of those patients made it into that on perhaps what some of us would call suboptimal doses of allopurinol? In other words, they had renal insufficiency that limited the use

of allopurinol, because that's a somewhat controversial area in terms of what is safe in terms of allopurinol dosing.

My second question I'll ask now, for the sake of time, has to do with the safety analysis, particularly the cardiovascular safety analysis. I'm curious whether, recognizing a limited number of patients, whether there was a post hoc analysis looking at the type of prophylaxis the patient was on, colchicine versus Naprosyn, et cetera, and was there any temporal association with flares reported by the patient?

DR. SCHWEITERMAN: I'm going to let Dr. Strand answer the question about allopurinol and then Dr. White, your second question about cardiovascular safety.

DR. STRAND: Well, by definition, subjects who were enrolled had to have failed allopurinol and their reason for failure was either that it had been contraindicated -- slide up, please -- or that they had had a history of hypersensitivity.

So you can see here that renal insufficiency, GI intolerance and allergy hypersensitivity were most of the reasons for why they had stated that it was contraindicated or, in fact, that it was ineffective.

Basically, I agree with you that the more effective dost of allopurinol tends to be above 300, but as we know from clinical use, it's rarely used beyond the 300 milligram dose.

DR. MIKULS: So can you tell me what dose the patients who, quote, "ineffective" or the renal insufficient group, what the average allopurinol dose was in those patients? I'm trying to get an understanding of whether these are the kind of patients we're going to want in real practice to be treating with this agent.

DR. STRAND: Well, as I understand it, the maximum dose that was tried in most of these patients wasn't going to be above 300. But there were plenty of patients, with the renal insufficiency, who had been dose reduced and were not going to be tried beyond 100 or 200

milligrams.

I think one of the points to be made, though, is that many of these patients, as you saw, were self-referred. They would not be the folks that would allow you to start allopurinol yet again because they had felt that they had failed it.

DR. WHITE: To address your question regarding the use of the concomitant prophylaxis medications and events -- could I have slide CV17 up, please? So this is the patients who were treated in the various three treatment groups with COX-2 inhibitors first, which actually turned out to be a fairly small percentage of the individuals. But as you can see, the events occurred more commonly in people not receiving than receiving them.

And if I can have slide 18, CV18, so these are all NSAID users, yes versus no, to contrast with colchicine, they had the option. Again, it was more common that patients had events in the non-users of NSAID in this case than in the

users. So there really wasn't a relationship nor was there one with colchicine use.

DR. O'NEIL: I got on the list for the next question.

It was stated that IgE antibody production was infrequent. Was there any tendency in those who did produce substantial IgE antibody against pegloticase to have more severe infusion reactions?

DR. SCHWEITERMAN: I'm going to let Dr. Lipsky answer that question.

DR. LIPSKY: As you know, measuring antigen-specific IgE is a formidable task and the company tried to do that quite well and achieved some results in that there were small fractions of individuals who had measurable IgE in the test they use above baseline. However, that didn't seem to correlate either with infusion reactions or with infusion reactions associated with elevated tryptase. So it was difficult to invoke a mechanism related to antigen-specific IgE, even in the individuals who actually had infusion

reactions associated with increased tryptase.

DR. O'NEIL: Thank you.

Next is Dr. Kaul.

DR. KAUL: Yes. On slide 16, you reported four deaths out of 110 patients followed for one year in the natural history study. What was the cause of death in these patients? I'm trying to understand whether these patients are dying from cardiovascular disease or non-cardiovascular disease.

DR. SCHWEITERMAN: Dr. Strand, you want to answer this, please?

DR. STRAND: Well, they were cardiovascular deaths predominantly.

DR. KAUL: Okay. I have another question.

While I recognize that the demographics of the pegloticase program was closer to the national history study, what proportion of the patients enrolled in the pegloticase program would be candidates for febuxostat?

DR. SCHWEITERMAN: DR. Becker, would you

care to answer that question, please?

DR. BECKER: There are several points, I think, relevant to that very appropriate question. As I alluded to in my presentation, it is fairly clear from the recent studies of allopurinol and febuxostat that they, in terms of efficacy, shadow one another in the length of time that effective reduction of serum urate will be accompanied by clinical response in terms of flare and tophus reduction, and that time, in general, is many months to several years.

May I see the slide, please? There hasn't been any directed studies with either of those agents, obviously, for allopurinol because of the fact that the groups selected for study here were allopurinol patients or allopurinol intolerant or ineffective patients.

But in the febuxostat development program, all of the RCTs were double blinded and, therefore, would have excluded patients who were not able to tolerate allopurinol. So in effect, the treatment failure gout patients were not

studied with febuxostat.

RB14, please. This is data taken, on the left-hand side, from a paper published by Ralph Schumacher. In patients who had participated in the allopurinol/febuxostat trial -- excuse me. This is the febuxostat trial, treated with febuxostat 80 milligrams a day and successfully over a period of up to five years.

In effect, this is the, on the left-hand panel, the reduction in flare percent and, in fact, one sees that even out to 250 weeks, that there's still a 20 percent residual tophus event. This compared to the data that you've seen in the responders with pegloticase, 81 percent complete response in the photographed tophi within a six-month period is quite remarkable.

I might add one other thing relevant to the previous discussion about duration of therapy, which is I see absolutely no reason why an agent like febuxostat could not be used after treatment with pegloticase in patients with treatment failure gout. Those individuals might be set back

in the course of their disease by a number of years by a course of pegloticase therapy. I'm saying, however, that I would still maintain the criteria that these patients have reached the clinical state of treatment failure.

DR. O'NEIL: Dr. Buckley?

DR. BUCKLEY: As a clinical rheumatologist, I think I'm trying to do what other people around the table are doing, which is trying to sort of walk through the numbers on the need for this drug and the response for this drug and the long-term issues.

So we're thinking now the proportion of people who might need this drug is around 50,000, but that number probably has changed since the approval of febuxostat. And then if we look at whatever that number is that moves forward to a treatment like this, it looks like, from the data you've presented, maybe only about 40 percent are going to be defined as persistent responders or less than that, and that's probably about six months. And if you take that data out further and

you lose people related to people who drop out for whatever reason, that number seems to be going down.

I'm also trying to understand the complexity of this infusion. So there are some infusions that are done quickly in an office and others where there's the possibility of infusion reactions and anaphylaxis that are actually quite lengthy.

So I think what I'm understanding you telling me is there will be a small group of people who will be eligible for this treatment. Of those, somewhere maybe less than 40 percent will be defined as responders over a period of six months to a year.

That infusion takes -- I'm not quite sure how long, but we're talking about an infusion that, I suspect, takes many hours moving forward. And then since that doesn't seem feasible for a long period of time, we would then -- we would sort of think of this as a drug that would be sort of remission inducing and we would move them to a

drug, probably not allopurinol, because of the numbers you showed us, but maybe febuxostat that would then hold that lower state of hyperuricemia.

But it seems like we are whittling this down between visibility and response to a smaller and smaller group of patients.

DR. SCHWEITERMAN: Well, those are very important questions. Let me say, first of all, that the estimate of the patient population is, in fact, about 50,000, but depending upon the criteria you use, depending upon the different types of analyses you can do, that number can change. So that's the best estimate and we've actually taken a fairly conservative estimate of that to begin with.

Secondly, the amount of benefit is, in fact, seen in approximately 40 or perhaps a little more than that patients, but it persists throughout the six-month and then the open label extension. In fact, if I could have the slide on the RCT OLE just to show you the continuation of benefit on out past 12 months. I think it's about

slide CS49 or 48.

The point I'm making is that there really isn't loss of benefit in these patients over a durable time course, that the benefit persists and that's been shown in the open label extension studies.

DR. BUCKLEY: But what proportion of -- you mean of the patients who benefit.

DR. SCHWEITERMAN: Right.

DR. BUCKLEY: They maintain that.

DR. SCHWEITERMAN: Right.

DR. BUCKLEY: But I think the question I'm asking you is what proportion benefit, and then of those, what number are going to drop out, as you've seen in your study, for maybe other reasons?

I'm not concerned that they'll stop responding. I'm concerned about the numbers that do respond and that will stay in the study given the feasibility of doing that and the complexity of their lives, knowing that in a clinical trial, those rates are going to be probably higher than

in the real world.

DR. SCHWEITERMAN: One of the more remarkable things about this study was the number of patients who returned for their visits after receiving the infusion to be able to benefit from the pegloticase therapy. It wasn't in some of the other typical trials you see, particularly for biologic agents, where patients benefit, but then don't pursue that benefit.

These are patients with crippling, severe disease for which there's dramatic immediate reductions and, as I showed, with the persistence of the response, they tend not to have any of the toxicities. The inconvenience to them is the infusion itself, which lasts couple of hours in an infusion center and then they go back.

It's been one of the things that has been notable about this, and that benefit tends to persist. And it's not an indefinite therapy, as we mentioned before, but, rather, one that can be viewed, as you mentioned, as induction therapy for these patients who have no other treatment

options.

So while there may be a small orphan population available for this drug and while half those patients or so may not benefit, you can identify them early and of those who actually respond, they respond immediately, they respond dramatically, and they respond durably.

So, Dr. Strand, do you want to comment?

DR. STRAND: Slide up, please. So this is just to show you what happens to the proportion of subjects who do go into open label treatment. As you can see, they're changing therapy, that we are continuing to accrue tophus complete responses in all of these patients, whether they're coming from placebo into pegloticase or they're staying with pegloticase therapy.

Then if we could go to SB43, please, I can show you overall what happens with pegloticase q2-week treatment group. Slide up, please.

So this is the total of 85 patients who were randomized to pegloticase q2-weeks and, as you know, 69 percent completed and there were 52

of those subjects who had tophi. Essentially, the persistent responders is, as you saw, 43 percent and within that persistent responder group, 58 percent of them had tophi and 62 percent of them had tophus complete responses within the randomized controlled six-month period of time.

When they went into open label, literally 80 percent of the 35 subjects in open label had persistent PUA responses and, as you can see here, too, they continued to accrue complete responses, or CRs, by tophi.

So I think you can see that up to 18 months of follow-up, 12 months in open label, and six months on the RCTs, the persistent responders continued to accrue benefit. And I could show you the pegloticase q4-week group. Those who were persistent responders have similar continued benefit.

DR. O'NEIL: We have time for just one or two more questions. We will take more questions for the sponsors after the FDA presentation. So we are going to have to cut this a bit short. And

the next question will be from Dr. Rosing.

DR. ROSING: The sponsors seemed to be appropriately concerned that pegloticase can produce oxidative stress and they mentioned that the rate of hydrogen peroxide degradation by red cells exceeds the generation by pegloticase therapy.

I just wondered what the data was to support that. And secondly, in the isoprostane studies, who was the subject group for those studies with pegloticase?

DR. SCHWEITERMAN: Dr. Hershfield will be happy to provide those data.

DR. HERSHFIELD: Those are very good questions and the importance is twofold. First, it's been postulated that urate is an important in vivo antioxidant. But the data for that is largely theoretical and more based on in vitro experiments, it's not in vivo. And the second issue is that hydrogen peroxide is produced as urate is oxidized by pegloticase and there is a concern that increasing the concentration of

hydrogen peroxide plus reducing the level of an antioxidant would increase oxidative stress status.

May I have the slide up, please?

These are two points that Dr. White summarized as bullets on one of his slides, stating that the rate of hydrogen peroxide degradation by red cells vastly exceeds the hydrogen peroxide generation by pegloticase therapy and that is the first question I will address. Then I will discuss the data and the patient population in which we looked at F-2 isoprostanes during pegloticase therapy.

Slide S62, please. Slide up, thank you.

This slide gives estimates of the rate of hydrogen peroxide production by pegloticase at a dose of 8 milligrams, in this case -- well, the issue of how frequent is not important right here.

But you can estimate from the specific activity of pegloticase and the size of the soluble urate pool and the rate of urate production that during the first 24 hours after

the first dose of pegloticase, hydrogen peroxide production would be maximal and at about a rate of 29 micromolars per liter per minute.

Thereafter, once the soluble urate pool has been eliminated, the rate of production of hydrogen peroxide is limited by the rate of urate production and degradation, and that would fall to a much lower level.

The rate of hydrogen peroxide degradation or the capacity of red cells to degrade hydrogen peroxide was determined in the 1980s in a number of studies, and I've cited one here in the Journal of Clinical Investigation, where it was shown -- and I won't go into the details, but I'll be happy to discuss it with you, if you'd like, that you can estimate from those data that at a hematocrit of 40 percent, the red blood cells have a capacity to eliminate hydrogen peroxide at a rate that is at least 100 and up to 3,000-fold faster than the rate at which pegloticase therapy would generate hydrogen peroxide. And this is an important analysis, because you have to recall that

pegloticase being PEGylated is retained in the intravascular system. So that all of the hydrogen peroxide generated would be in the intravascular space, where red cells would be the -- and catalyzed within red blood cells would be the predominant mechanism of elimination.

May I have slide S63, please?

This addresses the question about isoprostanes. Isoprostanes, I should point out, F-2 isoprostanes were discovered by Dr. Jack Roberts' laboratory at Vanderbilt in 1990 to be oxidation products of membrane associated arachidonic acid that are generated exclusively by free radical attack, predominantly oxygen radicals or oxygen-derived oxidants. And they've been validated in a number of different studies looking for the best biomarkers of oxidative stress status and have been validated as being very valid or - excuse me -- have been validated.

So what we did is we are conducting or have been conducting a Phase 2 trial of pegloticase, giving 8 milligrams every three

weeks, at Duke University. This is a trial that was sponsored by a grant from the Office of Orphan Product Development of the FDA. And this shows data from 21 patient and we provided frozen plasma samples from these patients to Dr. Roberts' laboratory at Vanderbilt to analyze F-2 isoprostanes by mass spectrometry. And we measured plasma uric acid here at Duke. And you can see, as has been shown, death during the first week of therapy, on the left-hand side of the slide, uric acid levels fall very rapidly down to less than 1 milligram per deciliter in all of the 21 patients.

During that time, these in red shows the percent change in isoprostanes from baseline and if anything, there's a drop of about 7 percent by the end of the first week, not an increase, as would be expected, if you were increasing oxidative stress.

These data on the right-hand side are taken one to two weeks after the last infusion, and that would be five infusions in 80 percent of

these patients. And they are analyzed here separately for the 15 patients in whom the response to pegloticase was maintained, so that over a 3.5 month period, their average of weekly analyses of plasma uric acid would be less than 1 milligram per deciliter, and there's a further drop to about 12 percent of baseline in isoprostanes. And these data, in the open circles are the patients who lost their response and uric acid increased to above 10 much earlier in the treatment, and, if anything, there is not any change statistically as to isoprostanes.

So in summary, I just want to say that this data suggests that pegloticase therapy could not increase the concentration of hydrogen peroxide and, secondly, that there is no increase in oxidative stress by this biomarker associated with pegloticase therapy over a significant period of time.

DR. ROSING: But who is the patient group in the second study?

DR. HERSHFIELD: The patient group is a

group of patients with treatment failure gout. And I must say that this group includes -- we were given permission to study patients with organ transplants and because of the conflict of interest on my part, I can't comment on the clinical response in these patients, but my colleague, Dr. Sundy, is here in the audience, if you wish to address that. But they were patients who would have qualified except for the fact that some of them had organ transplants before the pegloticase trial by Savient.

DR. O'NEIL: Okay. A number of the panel members have further questions, which we will have to hold until after the FDA presentation.

DR. SCHWEITERMAN: Madam Chair, Dr. Packer asked the question earlier that went unanswered. I know that time is short, but is it possible for Dr. White to answer his question before we move on?

DR. O'NEIL: If he can be quick.

DR. WHITE: Very.

So, Dr. Packer, the question was what was

the chance of losing contact with patients and not being able to determine if there was a cardiovascular event within the six-month RCT.

So as you recall, about 70 percent of the patients in each of the q2 and q4-week treatment groups completed; all the remainder actually went into an observational period, even if they declined participation, and none of the patients were lost to follow-up. So I would suggest that any serious cardiac event or death would have been captured, even if they stopped in that six-month period.

DR. O'NEIL: Thank you. We will now take a short 10-minute break. I ask the panel members to please remember that there should be no discussion of the biologic licensing application during the break among yourselves or with any members of the audience. We will resume promptly at 11:00.

(Whereupon, a recess was taken at 10:53 a.m.)

DR. O'NEIL: Please take your places and

we will resume the meeting. In this portion of the meeting, the FDA will present its information, and Dr. Rosemarie Neuner, from the Division of Anesthesia, Analgesia and Rheumatology Products at CDER, will present her presentation.

DR. NEUNER: Good morning. My name is Rosemarie Neuner and I am a medical officer in the Division of Anesthesia, Analgesics and Rheumatology products at the FDA.

Today, I will be presenting the FDA's review findings on pegloticase for the control of hyperuricemia and the management of refractory gout. My presentation will include a background on gout, the product's regulatory history, a brief summary of efficacy, as well as a summary of safety that will focus on the following three area: cardiovascular adverse events, infusion reactions, and immunogenicity.

As you've already heard, gout is a crystal-induced arthritis frequently associated with high hyperuricemia. But for the purposes of this presentation, it's defined as a serum uric

acid greater than or equal to 7 milligrams per deciliter. It's a common disorder affecting approximately five million people in the United States.

Based on self-reported population data collected by the 1988 to 1994 NHANES III survey, the prevalence of gout has been estimated to be approximately 2.7 percent in this country. It most commonly affects men over the age of 40 and post-menopausal women, with a male-to-female ratio of approximately 4-to-1.

The disease prevalence rises with increasing age to 9 percent in men and 6 percent in women over the age of 80. A variety of factors associated with hyperuricemia, such as obesity, hypertension, hyperlipidemia and metabolic syndrome, increase the risk for gout.

The management of gout is determined by the presentation of the disease. Acute attacks are most commonly managed by the variety of various agents, such as non-steroidal anti-inflammatory drugs, colchicine,

corticosteroids, or adrenocorticotropic hormone.

Chronic gout is treated by urate-lowering agents, such as allopurinol and probenecid. Recently, febuxostat was approved for this indication earlier this year. The goal for urate-lowering therapy is to reduce and maintain serum uric acid levels below 6 milligrams per deciliter to prevent crystal deposition and clear body stores of urate. Re-absorption of tophaceous deposits, however, is a slow process and may require years of chronic therapy.

Currently, allopurinol is the most commonly prescribed therapeutic agent to lower serum uric acid. However, its effectiveness is limited by a number of factors, such as the need for reduced doses in renal insufficiency, sub-therapeutic dosing resulting in failure to sufficiently lower serum uric acid levels, drug-induced toxicities seen in approximately 20 percent of patients treated with this drug, including hypersensitivity reactions in 2 to 4 percent of patients that have resulted in

fatalities.

Febuxostat, on the other hand, does not require an adjustment for renal dosing and may be a therapeutic alternative for patients unable to tolerate allopurinol. None of the presently approved urate-lowering agents have demonstrated in randomized controlled trials complete resolution of tophi.

Now, I would like to turn my attention to the product under discussion today. Pegloticase is a genetically engineered PEGylated mammalian uricase. Humans, unlike most other mammals, have lost the ability to produce functional urate oxidase. This product lowers plasma uric acid by metabolizing urate into soluble allantoin and hydrogen peroxide.

I would like to briefly discuss pegloticase's regulatory history. In 2001, this product was granted orphan drug status for the following indication: to control the clinical consequences of hyperuricemia in patients with severe gout in whom conventional therapy is

contraindicated or has been ineffective. The designation of orphan drug status was based on an estimated prevalence of 100,000 patients in this country with refractory gout.

Subsequently, a biological licensing application, or BLA, for pegloticase as a treatment for patients with refractory gout was submitted by the applicant in October 2008. This application was granted priority review status based, at that time, on an unmet medical need. A major amendment consisting of additional analyses to address cardiovascular adverse events in patients treated with pegloticase was submitted by the applicant, delaying the originally scheduled AC meeting.

The applicant's clinical development of pegloticase is based on two identical trials, studies 405 and 406. These were randomized, double-blind, placebo-controlled, parallel group studies in subjects with symptomatic gout and hyperuricemia, who were unable to tolerate or who had failed to respond to conventional

urate-lowering therapy.

A total of 225 subjects were randomized in a 2:2:1 ratio, stratified by the presence or absence of tophi to three treatment groups: pegloticase 8 milligrams every two weeks, pegloticase 8 milligrams every four weeks, and placebo IV infusions. Potential study subjects were prohibited from participating in these studies if they had a history of unstable angina, uncontrolled arrhythmia, decompensated heart failure, uncontrolled hypertension, end stage renal failure, or were post-organ transplant.

The primary endpoint for these two replicate studies was the proportion of subjects who maintained a plasma uric acid concentration below 6 milligrams per deciliter for at least 80 percent of the time during months three and six as compared to placebo.

The statistical analysis plan pre-specified that analysis of the secondary endpoints must have been conducted on pooled data from both studies. Subjects who completed these

studies were permitted to enter the open label extension study 407 in order to collect long-term safety data.

In the Phase 2 study, cases of hypersensitivity and infusion reactions were seen. To reduce the incidence of these events in the Phase 3 studies, all subjects received the following mandatory standardized pretreatment prophylaxis regime: 60 milligrams fexofenadine the night before study infusion, another 60 milligrams of fexofenadine with 1,000 milligrams of acetaminophen the morning of the infusion, followed by 200 milligrams of hydrocortisone IV immediately prior to the study infusion.

With regard to the demographic and disease characteristics of the patients who participated in these studies, the three treatment groups were generally well balanced in terms of their baseline demographics, gout disease characteristics and disease history. The majority of the patients had preexisting cardiovascular disease, including coronary artery disease,

cardiac arrhythmias and cardiac failure, left ventricular dysfunction. Additionally, a large number of them also had risk factors for cardiovascular disease, such as hypertension, diabetes, and dyslipidemia.

Of the 225 patients randomized in the combined studies, 212 or 94 percent were considered the intent to treat population upon which all the primary and secondary efficacy variables were conducted. Seventy-three percent of the intent to treat population also had evaluable tophi. The overall rate of study completion was 74 percent, with more placebo-treated patients completing the study as compared to patients randomized to pegloticase every two weeks or every four weeks treatment groups. Ninety-six percent of the patients who completed the studies went on to participate in the open label extension.

The major reasons for discontinuation were similar for the two pegloticase treatment groups, but different from placebo. The most

common reasons for early study withdrawal in the pegloticase treatment groups were due to adverse events, 19 percent in the q2 week versus 20 percent in the q4 weeks, and withdrawal of consent, 8 percent in the q2 weeks versus 7 percent in the q4 weeks.

Additionally, there were two deaths reported in the pegloticase every two weeks and one death in the pegloticase every four weeks treatment groups as compared to one death in the placebo group. The death of the placebo patient occurred post-randomization before the subject received study medication. Therefore, she was not included in the intent to treat population.

Next, I would like to discuss select findings from the efficacy analysis for studies 405 and 406. As you may recall, the primary endpoint for both of the Phase 3 trials was the proportion of subjects who maintained the plasma uric acid concentration below sis milligrams per deciliter for at least 80 percent of the time during months three and six as compared to

placebo. In both studies 405 and 406, significant proportions of subjects in both the pegloticase every two weeks and every four weeks treatment groups achieved the primary endpoint as compared to placebo.

There were a number of significant findings in terms of the secondary endpoints, which were analyzed based on pooled data from both of these studies. Forty-five percent of the patients with tophi who received pegloticase every two weeks had a complete resolution of their target tophus as compared to 8 percent of placebo treated patients at the week 25 time point.

Improvements were also seen in the number of swollen and tender joints. In the intent to treat population, the baseline mean number of tender and swollen joints was 23. Patients who received pegloticase every two weeks had a decrease of approximately 15 joints as compared to an approximate decrease of three joints in the placebo group at week 25.

The HAQ DI was examined as a measure of

physical function. For this measurement, a change in a score of 0.22 is considered clinically important. The subjects who participated in these studies had an overall mean baseline score of 1.2, consistent with moderate disability. Patients treated with pegloticase every two weeks had a 0.33 improvement in their score as compared to a 0.08 worsening in the placebo patients' score at week 25.

Pain was also assessed using a 100 millimeter visual analog scale. The overall mean pain score baseline was 48 millimeters for subjects in these studies. Patients in the pegloticase every two weeks group had approximately a 19 millimeter decrease in their pain score as compared to an approximate 3 millimeter decrease in the placebo group at week 25.

Since urate-lowering therapy increases the risk for disease flares, it was important to also look at the rate of gout flares over the course of the study. The incidence of gout flares

by treatment group is graphically depicted in this slide.

As you can see, during months one, two and three, more patients in the pegloticase every two weeks group had more acute flares as compared to the placebo group. However, during the months four through six, there was a decrease in the rate of disease flares in the pegloticase every two weeks group as compared to the placebo group, consistent with the reduced tendency to have gout flares over time.

To summarize the efficacy findings for pegloticase, a significantly greater proportion of patients treated with pegloticase every two weeks achieved normalization of plasma uric acid to below 6 milligrams per deciliter during months three and six as compared to placebo. Patients treated with pegloticase every two weeks as compared to placebo had significant reduction in tophi and in swollen and tender joints. The frequency of gout flares increased initially with pegloticase every two weeks. By months four to

six, the frequency of these events decreased below that of placebo. Significant improvements in pain and function in patients with pegloticase every two weeks as compared to placebo were also demonstrated.

I would now like to turn my attention to the safety of pegloticase. The safety data submitted in support of pegloticase contained 12-month exposure data from a total of 101 patients from both pegloticase does groups. Submission of the 120-day safety update brought the number of patients with 12 months of cumulative exposure data up to a total of 121 patients from both pegloticase dose groups, out of which 95 patients had 18 months of cumulative exposure to the product.

For the assessment of the safety profile of a drug or biological product intended as a treatment for a common disease, the ICH E1A guidelines specify that the safety databases should contain the following exposure data: 100 patients treated for one year, 300 to 600 patients

treated for at least six months, and 1,500 patients treated overall. However, these guidelines also specify that the target population size should be taken into account when determining the appropriate size of the safety database; for example, drugs or products intended as treatments for orphan diseases such as this one.

Review of the safety database for the pooled population of studies 405 and 406 revealed that nearly every patient reported having an adverse event while participating in these studies. Additional inspection revealed that treatment with pegloticase was associated with a higher rate of serious adverse events. The proportions of patients in the pegloticase every two weeks and every four weeks treatment groups who developed a serious adverse event were comparable, but were higher than that in the placebo group.

With prolonged exposure, the incidence of serious adverse events increased slightly to 28 percent and 32 percent, respectively, for the

pegloticase every two weeks and every four weeks dose groups.

Due to safety concerns related to the mandated prophylactic use of corticosteroids prior to each study infusion, we also examined the data for serious infections. As you can see, the rate of serious infections was between 5 and 10 percent. There was no difference between the study arms and the rate didn't appreciably increase with prolonged exposure to the product in the open label extension.

Since pegloticase is a therapeutic biologic agent, we were also concerned about the potential to develop an antibody response to the product, which could manifest as an infusion reaction. In spite of the standardized pretreatment prophylaxis regime, the proportion of patients experiencing an infusion reaction was increased to 26 percent in the pegloticase every two weeks group and 41 percent in the every four weeks group as compared to 5 percent in the placebo group. Most of the patients who had an

infusion reaction had it in the first six months of treatment, although there were some additional cases observed during the open label extension. These infusion reactions will be discussed in depth later in my presentation.

The proportion of patients who experienced an adverse event leading to early withdrawal during the controlled studies was similar for both pegloticase treatment groups, between 19 to 20 percent, but was much higher as compared to the 2 percent in the placebo group. These proportions increased slightly with prolonged exposure to the product.

During the controlled trials, a higher proportion of patients randomized to pegloticase every two weeks died as compared to patients randomized to pegloticase every four weeks group and the placebo group, which I will discuss next.

As shown in this table, there were a total of five deaths during the controlled studies 405 and 406. The death of the placebo patient occurred post- randomization, prior to the

administration of study medication. One patient died due to sepsis, while the remaining four deaths were due to cardiovascular events and occurred in patients who were at high risk due to multiple co-morbid risk factors.

As mentioned earlier in my presentation, more patients in the pegloticase treatment groups experienced serious adverse events as compared to placebo patients. Two of the system organ classes that contributed to the higher overall rate of serious adverse events in the pegloticase treatment groups were general disorders, administration site conditions, and cardiac disorders.

The higher rate for serious adverse events in the general disorders and administration site conditions for the pegloticase treatment groups was mainly due to infusion reactions, which are an expected adverse event associated with the product due to its immunogenicity. However, the 4 to 5 percent higher rates of cardiac disorders seen in the pegloticase every two weeks and every

four weeks treatment groups, respectively, as compared to placebo, were unexpected findings and shall be discussed next.

I've shown in this table there is an imbalance in the number of serious cardiac adverse events between the three treatment groups in the pooled controlled studies. There were four cases of serious cardiac adverse events in the pegloticase every two weeks group and three cases in the pegloticase every four weeks group as compared to none in the placebo group. This imbalance is due to a number of single cardiac adverse events, such as cardiac arrest, myocardial infarction, angina pectoris, and heart failure. However, arrhythmia was the only cardiac serious adverse event for which two cases were reported.

Further examination of the cardiac serious adverse events was undertaken by both the applicant and the agency. This table summarizes the applicant's independent blinded cardiovascular adjudication committee's post hoc review of these data. However, since Dr. White has already

discussed the adjudication committee's findings, I will go directly to our internal consultant's review of these data.

Based on his review of these cases, there were a total of five major cardiac adverse events that occurred in the pegloticase every two weeks group, three events in the pegloticase every four weeks group, and one event in the placebo group. In the ischemic cardiovascular disease category, there were two deaths in the pegloticase every two weeks group, one case of myocardial infarction, and one case of transient ischemic attack in the pegloticase every four weeks group, and one case of troponin leak in the placebo group.

Based on his review of these data, the agency's cardiology consultant concluded the following. The cardiovascular serious adverse events occurred in patients with preexisting co-morbid risk factors for major cardiac adverse events. The occurrence of these events is not only expected in view of the high prevalence of underlying cardiovascular disease in the patient

population who participated in these trials. There are too few cardiac serious adverse events to be able to allow detection of any pattern in their occurrence, resulting in a degree of uncertainty about the cardiac safety of pegloticase.

Next, I would like to discuss the infusion reaction data with pegloticase. As I mentioned previously, the higher rates of infusion reactions observed in the pegloticase treatment groups were not unexpected, since it is a foreign protein with innate ability to cause an antibody reaction. Twenty-six percent of patients in the pegloticase every four weeks group experienced infusion reactions that were moderate in severity as compared to 13 percent in pegloticase every two weeks group and 5 percent in the placebo group. Additionally, another 10 percent of the patients in the pegloticase every four weeks group experienced severe infusion reactions as compared to 5 percent in the pegloticase every two weeks group. The rate of occurrence of infusion

reactions peaked at dose three for the pegloticase every four weeks group and at dose four for the every two weeks group. Infusion reactions were managed by a variety of methods, which included supportive medical care and monitoring; slowing and/or stopping of the infusion, followed by either restarting or permanently discontinuing it; and, administration of IV fluids, diphenhydramine and corticosteroids, depending on the severity of the reaction.

There were five patients in the control studies who were sent to the ER for prolonged monitoring. One patient required a single dose of epinephrine for a moderate infusion reaction but recovered without sequelae. The most common reported signs and symptoms associated with infusion reactions included urticaria, chest pain/discomfort, erythema, pruritus, dyspnea, and flushing.

In the Phase 3 protocols, an infusion reaction was defined as an adverse event or cluster of adverse events that occurred during or

within two hours after the end of a study infusion. Due to the broadness of this definition, a wide spectrum of clinical signs and symptoms were associated with hypersensitivity reactions.

Review of these cases of infusion reactions revealed that some of them had features of allergic reactions, while others had characteristics of anaphylaxis. Due to concerns of possible cases of anaphylaxis, an internal allergy consultation was requested to help assess the infusion reaction data observed with pegloticase administration.

The allergy consultant employed the proposed diagnostic criteria by the NIH-Food, Allergy and Anaphylaxis Network Joint Symposium on anaphylaxis for unknown allergen for anaphylaxis that relies solely on clinical criteria. These criteria do not make a distinction for diagnosing anaphylaxis based on the underlying mechanism. Rather, the diagnosis is based on clinical findings and the knowledge of a drug's known

immunogenicity.

The NIH/FAAN clinical criteria for anaphylaxis are listed on this slide. They apply to three different clinical situations. The first definition is the most conservative of the three and it makes no assumptions based on inciting allergen.

The second definition applies to a likely allergen and requires at least two clinical signs, while the third applies to a known allergen and requires only a single clinical sign. For purpose of this analysis, the consultant applied the first definition of cases of infusion reactions contained in the safety database. This definition includes the acute onset of an illness with involvement of the skin or mucosal tissue and either respiratory compromise or reduction in blood pressure or symptoms of end organ dysfunction.

Among the cases of infusion reactions, there were seven cases that met NIH/FAAN criteria of anaphylaxis and safety database for the

controlled studies 405 and 406. Of these seven patients, one subject was able to complete the study, another subject continued to receive study infusions, while the remaining five subjects discontinued treatment.

The entire safety database for pegloticase was reviewed for additional infusion reactions that met the criteria for anaphylaxis. Based on the review of the safety data from the Phase 2, Phase 3 and open label studies, another seven cases of infusion reactions were identified that met criteria for anaphylaxis.

Three of these seven subjects continued to receive pegloticase infusions without additional infusion reactions, while the remaining four subjects, including the one subject who had a repeat infusion reaction four study infusions later discontinued therapy.

Based on her review if these data, the agency's internal allergy consultant concluded that there were a total of 14 cases that met criteria for anaphylaxis based on the NIH/FAAN

definition. The estimated frequency of anaphylaxis for pegloticase was 5.1 percent. By dose regime, the estimated frequency of anaphylaxis was 7.3 percent for the pegloticase every two weeks and 3.9 percent for the pegloticase every four weeks treatment groups.

However, these frequencies would likely have been higher but for the mandatory prophylaxis regime employed in the Phase 3 studies to prevent infusion reactions. None of the deaths in the pegloticase safety database were due to anaphylaxis. Treatment with placebo was discontinued in most of the cases of infusion reaction which met criteria for anaphylaxis.

However, five of these patients did receive additional pegloticase infusions. Three of them had no additional reactions, while the remaining two patients continued to have these events.

The immunogenic potential of pegloticase was also examined as part of the safety review. Approximately 88 percent of patients in the

pegloticase every two weeks group, 89 percent of the patients in the pegloticase every four weeks group, and 20 percent of the placebo patients tested positive for anti-pegloticase antibodies on at least one time point over the course of the controlled study. A dose-dependent relationship with antibody titer was not apparent.

Since the presence of pegloticase antibodies could potentially reduce the effectiveness of pegloticase, we looked to plasma uric acid responses in patients positive for pegloticase antibodies and, as shown on this slide, found that the response rate did, indeed, decrease with increasing anti-pegloticase titer.

Since antibody status can also adversely affect the safety profile of a biologic therapeutic agent by immunemediated events, we also looked at the incidence of infusion reactions that occurred in patients who tested positive for anti-pegloticase antibodies and noted that the rates of infusion reactions increased directly with increasing anti-pegloticase titers.

To summarize the safety conclusions in the randomized control trials, a numerically higher rate of death was observed in the pegloticase every two weeks group as compared to the every four weeks and placebo groups. These deaths were due to infection and cardiovascular events and occurred in patients with multiple underlying risk factors. A higher rate of serious cardiovascular events was observed in both pegloticase treatment groups. A higher rate of serious infusion reactions was also seen in the pegloticase every two weeks group as compared to placebo. Approximately 5 percent of patients met criteria for anaphylaxis.

Pegloticase was observed to be highly immunogenic, with zero conversion rates of 88 percent in the very two weeks group and 89 percent in the every four weeks group over the course of the studies.

Based on our review of the pegloticase application, treatment with pegloticase every two weeks resulted in statistically significant

improvements in both plasma uric acid and clinical responses. However, a decrease in efficacy was associated with increasing levels of anti-pegloticase antibodies. A numerically higher rate of death in the pegloticase every two weeks group was observed compared to the every four weeks group or the placebo group. These deaths were due to infections and cardiac events.

Treatment with pegloticase was associated with higher rates of serious adverse events and these reflected a higher rate of serious infusion reactions and cardiac serious adverse events. A numerically higher rate of cardiovascular events was observed in the pegloticase treatment groups. The presence of anti-pegloticase antibodies was associated with an increased risk of infusion reactions.

Approximately 5 percent of the patients with infusion reactions met clinical criteria for anaphylaxis. In view of the documented adverse events, careful consideration of benefits and risks is essential to determine with pegloticase

should be approved.

Thank you.

DR. O'NEIL: Thank you. We will now take questions for the FDA.

Dr. Packer?

DR. PACKER: I have one question on how you analyzed the efficacy for the secondary endpoints. As I understand it, if someone dropped out, they were considered a non-responder for the primary endpoint.

But how did you analyze dropouts for the secondary endpoints?

DR. NEUNER: My statistician is here and she can address that succinctly.

DR. DAVI: Hi, my name is Ruthanna Davi. I'm an FDA statistical reviewer. For most of the secondary efficacy endpoints with missing data, a last observation carried forward approach was used.

DR. PACKER: And does that mean -- is it because when someone dropped out, they didn't undergo the assessments?

DR. DAVI: The data could be missing for -- for the most part, I think the answer would be yes. But for whatever reason, the data was missing. It was imputed with the last observation carried forward.

DR. PACKER: Okay. I'll just assume that the data would have been less striking if you had followed the same statistical procedure for the secondary endpoints that you did for the primary.

DR. DAVI: I think that's probably a safe assumption.

DR. O'NEIL: Next question from Dr. Buckley.

DR. BUCKLEY: I'm trying to understand the pattern of response to this treatment. It's obviously very dramatic for some patients. Normally, when we think about response to a treatment, we think it might be sort of a bell-shaped curve. Some people get a little, some people get an average, and some people get quite a response.

It seems this treatment is a little

different, but it's hard for me to gather that from mean data. But it seems like in this treatment, you can sort of qualify it. Because of the antibody development, there are going to be sort of winners and losers. There are going to be people who have a better chance of response because they don't develop much in the way of antibodies and those who are unlikely to respond. And when I look at the data that way, it looks to me like about 40 percent, somewhere between 40 and 50 percent are going to be in that responder group.

Do you think that's a fair analysis? If I was talking to a patient about this treatment, would I say, "Well, there are people who respond and people who don't respond because of antibody development and it's going to be hard to predict that until we start treating you?"

Do you think it sort of divides into -- and within the responders, probably, a bell-shaped curve, but within the non-responders, more of a flat response rate.

DR. NEUNER: That's an interesting view of the data and I think I would have to agree with you, that's how I would approach it clinically, on a patient-by-patient basis. There's no way to predict who is going to end up making antibodies to the product, and as we saw from the sponsors presentation, that the antibodies did affect the efficacy of the product. And so I guess that the best way to find out would be to challenge a patient first with it or administer it and see what would happen.

DR. BUCKLEY: So would it be fair to say, then, approximately 40 to 50 percent of the patients are going to respond on the two-week protocol, but about everybody has a 30 percent risk of a serious adverse event, and about 26 percent of those are going to be significant infusion reactions?

Again, if I was discussing risk versus benefit with a patient, would that be an accurate description?

DR. NEUNER: Based on the data that I've

reviewed, I would have to agree with your assumptions.

DR. O'NEIL: The next question from Dr. Burlington.

DR. BURLINGTON: Actually, two questions and they both go to how we count adverse events. In the FDA's overall conclusions and in the presentation, you really focused on the deaths that occurred during the randomized period. The sponsor presented both data on during the randomized period and during the follow-up period, in which the small number of events seemed much more balanced.

So the question is, was there an a priori decision or rule about how to count deaths as adverse events or are we just seeing different views of the same information all constructed post hoc?

DR. NEUNER: Actually, if you look at the AC debriefing package, I put in a table of all the deaths that that were included in the original submission, as well as the 120-day safety

database. But for purposes of this presentation, I only included the deaths that occurred during the randomized placebo-controlled studies.

I did not include the two patients that withdrew due to adverse events and that subsequently died four months after their last dose of pegloticase, because I thought it would kind of muddy the data. I think it was just a decision, based on my part and my team leader's part, to decide what needed to go in for the purposes of this discussion.

DR. BURLINGTON: Okay. And the second sort of related question is in terms of the NID/FAAN definition of anaphylaxis versus the terms the sponsor used and collected. My understanding is this is intended to be a case definition which is inclusive and however we look at what is anaphylaxis -- and it's bad, in and of itself, to have anaphylaxis. I don't doubt that. But do we know the predictive value of this case definition for major morbid or mortal events?

DR. NEUNER: My allergy consultant is

here and she can address that.

DR. LIM: Hi. I'm Susan Lim. I'm a clinical reviewer in the Pulmonary and Allergy Division at the FDA. So these case criteria have not been studied in a prospective study design. So in that sense, we don't know what the predictive value is for a major mortal event.

But I think one of the major principals that went into developing these criteria is that anaphylaxis is inherently unpredictable and because you have multi-organ, multi-system involvement, that, by definition, is serious and potentially life- threatening. So I think it's reassuring that in this pegloticase case safety database, there weren't any apparent fatal events, but I don't think we can be reassured that that wouldn't be the case in the future. I think it's just a risk that needs to be acknowledged.

DR. O'NEIL: Dr. Siegel?

DR. SIEGEL: I was going to respond to the first question about the way that the FDA analyzes safety data, for instance, the deaths.

So we don't go into analyzing a database like this with a pre- specified way of analyzing the safety data. We explore the data for potential safety signals.

We consider the control trials particularly informative, because there's an internal control, but we also look at the long-term extension data, because it provides data on a longer exposure. So what Dr. Neunan was focusing on was the area where we did have the control data, but both, of course, are valuable.

DR. O'NEIL: The next question is from Dr. Weisman.

DR. WEISMAN: In your opening comments about gout and the epidemiology, do you think that febuxostat is going to make an impact on the natural history of these patients in the future and what will be the -- and what would be the pool of patients that would be eligible for this drug?

Now, we know that, of course -- and I fully understand that this particular group of patients that were in the trial are not candidates

for febuxostat. The sponsor has commented in that regard. But going forward, what do you think is going to happen to this? Then I have another question.

DR. NEUNER: That's a very good question, because as you may recall from my presentation, when we gave this priority review, it was based on, at that time, an unmet medical need, because febuxostat had not been approved for marketing in this country.

Now, that it's available, there's another therapeutic option for the patients who are unable to tolerate or fail to respond to allopurinol. But that does not mean that this product does not have additional efficacy for patients such as those with severe tophaceous deposits.

I also did mention in my comments earlier that the treatment of tophaceous disease is very time-consuming. You have to be very, very patient. I don't recall, in 20 years as a rheumatologist, that I've actually ever seen a tophi disappear, and I was trained by Stanley

Wallace, who used to write the chapter and the primer of rheumatology, and he was a big proponent of increasing the allopurinol dose up as far as the patient could tolerate it based on their renal parameters.

So I think that time will tell, that it will depend on practice preferences and how people will utilize these various products. I think it's too soon to make any judgments or calls.

DR. WEISMAN: My other question is a little bit far afield from the first, and, that is, the sponsor has proposed a registry. How can this registry be mandated? Is that possible to mandate a registry in the United States or should the registry be voluntary with the issues that concern us with all kinds of voluntary activities?

What is your view of the registry and should it be mandated?

DR. NEUNER: I'm going to defer to Dr. Siegel on that question.

DR. SIEGEL: I'll take a start and there may be other people from the agency side who will

want to weigh in on this, as well.

There are situations where registries can be mandatory. My understanding is the Tysabri involves a mandatory registry. There, it's a situation where patients are followed carefully for the major risk there, which is progressive multifocal leukoencephalopathy. So the intent of the registry is to reduce risk, but as part of it, it ends up being a mandatory registry where all the data can be captured on all the patients treated. There may be other ways that registries can be mandated, but it is a possibility in some cases.

DR. O'NEIL: The next question is from Dr. Nelson.

DR. NELSON: I actually have two questions, as well, and perhaps the first one could be answered by you, as well as by the sponsor, if that's possible.

In the sponsor's briefing document, at Table 47, they go through a group of patients who they -- it says that they were in the open Phase 2

and the OLE study, but they have study numbers that would suggest that they were part of one of the randomized trials, they're number 405s, and I'm not sure how that exactly works.

But there were several patients in those studies who suffered from DVTs and when you look at their data in their slide 129, there's only one patient who suffered from what sounds like a venous thrombotic event. And I wonder if there's any concern for that kind of data misalignment and if there's something that we have to look a little bit more carefully at.

DR. NEUNER: That's a good question and I would like to ask the sponsor what they think about it.

DR. SCHWEITERMAN: Slide up, please.

The question had to do with the number of adverse events particularly regarding DVTs in the open label extension study. I'm not sure that this is the slide that shows that.

But the open label extension study itself was not a randomized study. There was not a set

randomization pattern beforehand. Moreover, there was not a set dose. It was investigator-patient elected along the way, and the patients continued at their pleasure with the physician with regard to continuing therapy or not or even switching doses in some particular cases.

Slide up, please. This is the slide with the deep vein thrombosis.

So in our assessment of the data using these definitions, keeping in mind that there were patients who started on one dose, went to another, sometimes discontinued, these are the data that we had.

We could talk with the agency about their determinations, as well.

DR. NELSON: I appreciate that. I just get concerned, because we were talking about thrombosis as a potential issue when it comes to many of these non-fatal or even fatal cardiac events. And there aren't many links between a lot of these diseases, except ischemia, and thrombosis certainly would be something to be concerned about

when you're trying to link those together.

My second question was actually about the REMS plan, as well. It looked different than the REMS that was presented in the sponsor's documentation. I mean, it's good, I think, personally, to have some more rigorous data collection like they're doing.

I guess what I wasn't clear about, and I don't know if FDA wants to comment on this as well, is it's not just a mandatory question. It was more was the intent of this registry just to be their version, or your version, of a Phase 4 study where you're just kind of observing patients post-marketing, or was it really to drive practice and to have patients -- I mean, you use the word "certification" of physicians and patients.

So I don't know if that meant to be certified like you take a quiz and you kind of sign on a line that says you're only going to enroll patients that meet certain criteria, thus, people who have unfortunate disease who don't quite meet the degree of need that this drug would

suggest or those that have co-morbidities that were of any real significance that would preclude them from entering this trial, would, in fact, be not enrolled and not given the drug and would also allow you to do fairly rigorous follow-up, including all the things that we'd like to look at as these additional endpoints as time goes on?

DR. SIEGEL: Actually, this is the FDA section and it was addressed to the FDA. So the FDA hasn't reached a final determination about whether REMS will be required or what the nature of the REMS is.

The sponsor presented their ideas on a registry and the FDA will be very interested in the committee's views about what would be appropriate post-marketing studies to do and you'll see that's one of the questions in the list. But we haven't had extensive discussions on exactly what it should be.

DR. O'NEIL: The next question is by Dr. Kaul.

DR. KAUL: Yes. How do you account for

the discrepant efficacy response with q4 weekly regimen in protocol 405 versus 406? You have a 20 percent response rate in 405 versus 49 percent in 406, and there is no overlap in the confidence interval. And I have a follow-up question to that.

DR. SIEGEL: I'll take a crack at that. It's unexpected, of course. These are replicate studies, so you would have expected to see similar results. It's possible that there's some variability in responses and we're just seeing statistical noise, as it were.

But I think another possibility is that we're using a categorical endpoint rather than numeric endpoint and it's looking at the percent of people who were able to maintain their serum uric acid and plasma uric acid consistently below 6. And as you saw from one of the graphs, in the q4 week arm, there's a tendency for the plasma uric acids to come back above 6 at some point during the time course. So that may contribute, as well. But we don't have a good explanation for

the difference in efficacy.

DR. KAUL: So the follow-up question is that the sponsor has asked for a q2 weekly drug regimen. In your estimate, do you think that's the more -- that that dose has a more desirable benefit-risk profile, if you look at all the other adverse events? I really didn't see any compelling differences except for the two big ones.

Even though the numbers are very small, you have an anaphylaxis rate of 7.3 percent with q2 versus 3.9, nearly a twofold increase, and you have a death of four percent in the q2 versus one percent in q4 weeks.

So how do you answer that question? Which, in your judgment, is a more desirable benefit-risk profile?

DR. NEUNER: I would like to answer to that.

I think, as the clinical rheumatologist, when you have a product where you're not really sure about the response or the safety profile, you

will want to see some definitive clinical benefit when you administer the product. And in the q4 group, as you may recall, on the sponsor's slide, they did not capture the secondary endpoint for tophus resolution, which is very important, particularly in this patient population given their risks of co-morbidities for cardiovascular events and the fact that they need to take steroids prior to the administration of the infusions.

They should be getting some clinical benefit from the product. So even though that the q4 captured the primary endpoint, the mere fact that it failed to capture the resolution of tophi was clinically important.

DR. KAUL: But how do you counter that with the side effect profile? I mean, it's a judgment call, obviously. We are relying on a secondary efficacy endpoint against a safety endpoint, which some may argue perhaps might trump it.

DR. SIEGEL: I think Dr. Neuner went over

some of the considerations. The sponsor has proposed the q2-week regimen. So that's their preference.

We are very interested in what the committee thinks about the potential risk-benefit of the two different dose regimens. Clearly, with respect to the tophi, which was a secondary endpoint, it was a higher rate of resolution with the q2-week regimen.

The rate of infusion reactions was higher with the every four week regimen than the every two week regimen. But we are definitely open to comments from the committee about the consideration for other doses.

DR. O'NEIL: Dr. Stine?

DR. DAVI: May I make one comment?

DR. O'NEIL: Yes.

DR. DAVI: I wanted to caution you. The results given for the primary efficacy endpoint in that table are confidence intervals for the difference between the treatment group and the placebo, not the treatment group itself.

So the fact that those two confidence intervals from the two different studies are distinct are not necessarily indicating that the point estimates from one study is distinct from the other.

Then a corollary to that is this would be a cross-study comparison and I'm sure you're aware that can be problematic because there's no randomization there.

DR. O'NEIL: Thank you.

Dr. Stine?

DR. STINE: I'd just like to make a couple of comments and then raise a question. I think it's important, particularly when we look at the issues of the secondary study, knowing that you're taking the drug isn't going to -- you're not going to be able to make your uric acid levels change, but it could certainly influence how you respond to how well do you feel and are you feeling more mobile and more comfortable. And certainly given the presence of these infusion reactions, I don't think somebody that had those

would know. I do think somebody that had those would certainly know that they were being treated. So in terms of the blinding, I'm a little concerned about the loss of blinding for some of the endpoints because of the nature of the therapy.

With regard to Dr. Kaul's comment, I noticed the non-overlapping confidence intervals, as well, and being a statistician, that always sort of gets your eyebrows up. And if, indeed, those are confidence intervals for the difference, I would encourage you to use slightly different labeling or something, because I had the same impression he had.

But the other answer to that question, too, is that the study has not been adjusted for multiplicity and when you see zillions of confidence intervals, there is going to be a chance something doesn't overlap simply by chance alone, which then comes to the question I have, namely, the small size of the study.

When I first looked at the study, having

looked at -- this is my third, I think, panel meeting, I thought there was a zero missing from the end counts. I'm used to seeing 850 in a safety study, not 85. And so I was particularly taken by that and so I was going to raise the question of what are the guidelines for a safety study in a treatment such as this, particularly a treatment that has some question about its safety profile with regard to sever cardiovascular types of events. Eighty-five just strikes me as quite small. And I was curious to hear from the FDA, given that there are these guidelines talking about 1,500 patients treated overall, have there been other situations where the FDA has recommended not adhering to those guidelines and instead sort of -- are we setting a precedent here by ignoring those guidelines or has that precedent already been broken in the examples of other sorts of studies?

So I think it would be useful to have some continuity across different studies as to how a committee steps away from those sorts of

guidelines, particularly when an issue of safety is involved.

Then, finally, another question is I get the impression from the FDA's response that the only way we can find out who is going to be a responder to this drug or not is just to zap them with the drug. In these days of proteomics and genomics and all, I would think there would be other perhaps more benign ways of testing who is going to be a responder and who is not going to be a responder other than jamming this into somebody and let's see what happens.

Now, I'm pretty naive as far as these things go, but my impression would be that there might be some other sort of way of trying to assess whether that's possible, given that we do have these other concerns about safety. Thank you.

So the two questions were precedent for smaller sample sizes and then this issue of is really the only predictive way to see if this is going to respond is to try it out.

DR. SIEGEL: Right. So these are really important questions and I'll try my best to address them, but there are no clear-cut answers and we're interested in comments from the committee about whether they think the size of the safety database is adequate.

Let me make a couple comments. You said this was a safety study. These were actually studies of efficacy. We power studies for efficacy based on assumptions for efficacy, the percent of responders who are expected in the treatment arm, the percent in the control arm, and we examine the size of the study based on whether it's adequately powered to meet the study objective, which is to show efficacy.

Now, of course, we find out a lot about safety from the randomized efficacy studies, because you can compare adverse event rates in the treated patients with the controls. But the requirement for randomized safety studies is not as clear-cut or straightforward as the requirement for randomized efficacy studies.

Dr. Neuner went over for you the size of the safety database that's required for common diseases, chronic diseases, and that would be 1,500 patients treated overall, 300 to 600 patients treated for six months and 100 patients treated for a year. For products that we review that are immunosuppressive, we actually expect a larger safety database, actually, 1,500 patients treated for at least a year at the expected dose.

This is a somewhat different situation. It doesn't -- it's an orphan disease with a smaller patient population. So it's an open question about what the size of the safety database should be.

When the clinical development program was being developed, we didn't know exactly what the safety issues would be and I can't say that we anticipated that we would see this number of cardiovascular adverse events. Looking back on it, you could say that it should have been expected based on the co-morbidities present. We didn't expect that there would be differences in

rates between the different events.

So we'll be very interested, as the day goes on, in hearing the committee's views on what the size of the safety database should be and if the committee believes that this is not adequate, then we'd like to hear what the committee would believe is adequate.

I'd make one last comment with respect to that. The ICH E1A guidelines were developed, in part, based on the rule of three and similar considerations for assessing safety. So the rule of three says that if you have 300 patients treated and you don't see any serious adverse events, then the rate of -- any of a particular kind of serious adverse event, then the rate of that particular adverse event, based on the 95 percent confidence interval, can be confidently stated to be less than 1 percent.

So a large safety database, if you don't see anything, can be used to rule out an occurrence. But with relatively common events in this patient population, cardiovascular events,

getting a large uncontrolled database, it's not clear exactly what that would teach you. And doing it in a controlled manner is complicated, because to rule out even a 30 percent increase in the rate of cardiovascular events can take 10,000 or even 20,000 patients.

So these are all important questions and we really are counting on the committee to provide us your thoughts about what an appropriate safety database should be.

DR. ROSEBRAUGH: Can I just add something to that to get a little more to whether you're setting a precedence or not? There are some drugs that we require two years of safety and we want to see a lot more people. There's others where we've had less than 100 in less than a year. It just kind of depends, like Jeff says, and particularly with orphan indications, it can be kind of tough to get long-term data.

You did have another question about with our new sophistication, can't we just predict who is going to respond. And you know I'm a clinical

pharmacologist by training, so you've hit a subject dear to my heart and, unfortunately, we're not there yet.

DR. O'NEIL: Dr. Mikuls had a question.

DR. MIKULS: My question actually is a follow-up to that, it so happens. Twenty percent of the placebo population had at least low or moderate titers of the antibody to the drug, which raises a question whether there are patients in the treatment population who were sero positive at baseline and whether that was at all predictive.

The idea being, obviously, that if you have antibody -- it may just be a specificity issue of the assay, but if there's antibody at baseline, does that predict either immune reactions or loss of response over time.

Has that been looked at? Were the placebo patients who were sero positive, did they go into open label follow-up with drug? We'd know something about them. I'd suspect the numbers are small. But you see where I'm going with the question.

DR. SIEGEL: I'll start and then we may need to ask the sponsor to provide more information.

You point out correctly that you don't expect to see any product antibodies in the placebo group, but there was a rate. And a couple of potential explanations, it's possible that there are antibodies in the general population that cross-react with perhaps the sugars in this product, because it does have polyethylene glycol. The other possibility is it's a sensitivity issue and it's a very sensitive assay that picks up people who really don't have meaningful antibody responses.

The 20 percent, I believe, is over the course of the whole study. For the patients at baseline, there were very few patients who had antibodies at baseline and I don't know if those few patients had infusion reactions. Perhaps the sponsor can shed some light on that.

DR. SCHWEITERMAN: Slide up, please.

It's a very important question, one we

evaluated immediately upon seeing the data. The antibodies, as I mentioned in my presentation to the pegloticase directed against polyethylene glycol. And so the question obviously was -- and this is because, as Dr. Siegel briefly mentioned, there exists in the marketplace different products with polyethylene glycol, toothpastes and so forth that exist. And so this is slide showing baseline and pegloticase subjects who had infusion reactions as a function of whether they had anti-pegloticase antibodies at baseline.

The first graph shows subjects with infusion reactions and then who were discontinued. As you can see, there was a relatively small number. It's very difficult to make any sort of inference. But one of four of the placebo patients, for example, had an infusion reaction, 8 of 15; 1 of 13 of subjects in the q2-weekly. And then with dose with no anti-pegloticase antibody at baseline, again, small numbers, the third row down, 29 percent, 38 percent, and 3 percent of placebo.

Slide down.

So furthermore, to answer your question -- slide down, please -- we looked at the very first -- the patients who had infusion reactions at their very first dose with regard to severity, including the two patients I mentioned who had requirements for either going to the hospital, to the ER for monitoring -- as I mentioned, they all recovered -- or any other associated things that were suggestive of anaphylaxis.

They were only two such patients in the entire database that met that criteria, with just slightly more patients with infusion reactions overall, approximately five or so. And so of those two patients, we looked very carefully at the baseline antibodies. One was at an antibody level of 1:270, very low level baseline titer. The other one was at 1:2430.

Again, the evidence from these data and from these baseline studies is that there is no interaction, there is no increased risk for

whether you have baseline antibodies at titer or not.

If I can, then, there's a very important question about -- that I think we want to clarify with regard to infusion reactions in general and as they occur over the long term.

It's important to understand how these break down, because the situation isn't that once you respond, you necessarily are at the same risk for when you don't respond. In fact, response itself is an indicator not only of long-term response, but of the unlikelihood of actually experiencing reaction; hence, our very close attention to the serum uric acid.

If I could show some of those data from Dr. Strand, we could further explain that.

DR. O'NEIL: I guess that's okay, if we can quick, because we're running short on time.

DR. STRAND: I just want to clarify one point, and that is that we've been talking about febuxostat and this treatment failure population, and this is not a population like the gout

population enrolled in the febuxostat studies. And, in fact -- slide up -- in the febuxostat studies, those subjects who failed allopurinol subsequently went into the highest dose of febuxostat open label and, actually, only 41 percent of those subjects responded in terms of achieving a uric acid level of less than 6.

So we just wanted to point out to you that these are, in fact, different populations from the subjects who have been studied with either allopurinol or febuxostat in those trials. And this is a gout population that's very different from the ones that we've seen in other studies.

In terms of the long-term follow-up, I had shows you before the PK2 group and that was SB43, and the point there is that if the persistent responders-- actually, they do not have infusion reactions -- slide up -- and they are not the ones who will have, shall we say, the risk that you've been concerned about. They have persistent benefit. If they continue to have a

plasma uric acid response at three months, then they maintain that response over time for as long as 18 months.

So, in fact, maybe it is that we have to give the therapy, but most of these infusion reactions have been relatively well tolerated. They have resulted in discontinuing therapy. But if we had been monitoring the plasma uric acid -- serum uric acid levels, then all but two of these infusions would have been avoided completely. And remember, again, that only one of them occurred in a persistent responder in the pegloticase q2-week group.

DR. O'NEIL: We're going to need to move quickly along here. I'm going to take one more question from Ms. Aronson, and then the other questions we will hold until the public hearing is completed.

MS. ARONSON: Thank you. I'm trying to decipher the effects of the use of prednisone and hydrocortisone versus the drug. In particular, I noted that there may have been some potential

unblinding after the third dose and that 45 percent of the drug arms used concomitant prednisone versus the placebo using 30 percent. And I'm just wondering what that effect had on the results.

Also, in relationship to the two-dose regimen, they were getting more hydrocortisone throughout the time period. I also wonder about the prophylaxis required treatments. I looked up hydrocortisone and the side effects. You have sodium retention and problems with wounds healing and I noticed a couple of amputations. So that was a concern.

So just thinking of the quality of life with the prednisone and what happens after the end of the treatment and does that level of prednisone have to continue after the study drug is stopped?

DR. SCHWEITERMAN: Slide up, please.

The question about concomitant medications is shown in this particular slide. This is the breakdown of patients who received colchicine less than .6 milligrams per day and

greater than 1 one milligram per day and the distribution of this across the two treatment arms. It was a fairly low percentage. We did not determine any relationship between the use of these drugs and the kind of adverse events you mentioned. Actually, we looked quite a bit into other things, like antibody titers and so forth.

Dr. Strand, did you want to add to this?

DR. STRAND: If we can go to the next slide, please, it's B55.

As you can see, it is pretty well distributed across the treatment arms and I remind you that we had some antibody response in placebo. We also had two placebo patients who had tophus resolution.

But, in fact, we think that that was because of the way the photographs were taken, that it wasn't, in fact, a real tophus response. But overall, as you can see here, these are pretty well distributed and don't really show significant differences.

DR. O'NEIL: All right. Thank you,

everyone. And we will now break briefly for lunch. We will reconvene again in this room in one hour. At that time, we will have the open public hearing, followed by further discussion.

I would like to remind panel members once again that there should be no discussion of the meeting during lunch among yourselves or with any members of the audience. Thank you.

(Whereupon, a lunch recess was taken at 12:10 p.m.)

A F T E R N O O N S E S S I O N

DR. O'NEIL: Good afternoon. We will begin the afternoon session with the open public hearing. First, Nicole Vesely will read a statement.

DR. VESELY: Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way so every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

We would just ask that anyone who is a registered speaker to come near the podium so when

your name is projected, you can approach the microphone.

DR. O'NEIL: Thank you. The first speaker, who will have five minutes for comments, is Herbert Baraf.

DR. BARAF: Members of the Arthritis Advisory Committee and members of the FDA, I am a practicing rheumatologist in the Maryland suburbs of Washington. I have been a clinical investigator for Savient and I am here today to present my personal views on pegloticase.

First and foremost, I am a clinician involved in the day-to-day management of patients. Patient care consumes more than 90 percent of my time. I have conducted clinical trials in rheumatology since 1981. I have participated in over 300 trials and have witnessed many developments in the therapeutics of arthritis during this time.

My experiences with the pegloticase program were extraordinary. I would like to share some of my observations with you today. Our site

enrolled six patients in the Phase 2 program. Among the patients was a 67-year-old oncologist, Dr. S, with a history of tophaceous gout, allopurinol allergy, and intolerance to colchicine and NSAIDs.

He was referred by a colleague for potential enrollment in the trial. I knew Dr. S personally and a few days later, I ran into him at a local hospital. He described the difficulties he was having with his gout. He was in constant pain, unable to wear most of his shoes due to enlargement of the feet with tophi, and was experiencing frequent flares of gout in his hands.

I noticed prominent tophi on his hands and thinking images of his hands would be useful in teaching young physicians about gout, I asked his permission to photograph them with my Palm Zire 71 at the time.

Six weeks later, he was enrolled as our first patient. The Phase 2 program was a 12-week dose-finding protocol. At the end of Dr. S' participation, I was astounded to find that tophi

on his hands had resolved, and I handed something out to people on the panel, and page 3 has those images.

Tophi do not resolve in three months, not even in three years, with standard treatments. Excited about what I had observed, I re-photographed him and shared the pre and post treatment photographs with the sponsors, since such a rapid dissolution of tophaceous deposits was a phenomenon previously unheard of.

I subsequently made a similar observation with pre and post treatment photographs of a second patient. These two observations were eventually published and in the Phase 3 program, the sponsor tracked the responsive tophi to pegloticase, making it a secondary endpoint of the trial.

In Phase 3, our site was successful in randomizing 13 patients. Nine patients completed all of their infusions. Two were on placebo and showed no response. But all seven completers on active drug responded. Eight of nine patients who

completed the double-blind phase of the protocol went on into the open label extension.

I would like to tell you about two of them, both allopurinol allergic. The first was an 81-year-old woman, Mrs. J, referred by a neighboring rheumatologist, she presented with large tophaceous deposits on her hands and open ulcerated tophi on her both feet.

Her daughters brought her to the office in wheelchair. She could not walk on these lesions and had become increasingly dependent on her children. She was being managed unsuccessfully at a wound center, receiving hyperbaric treatments to her feet.

In less than 12 weeks on pegloticase, her foot ulcerations healed; and, by six months, her hand tophi resolved. Photographs are also included in what you have. She became ambulatory and regained her independence.

A second patient in Phase 3, Mr. L, a 46-year-old engineer, came to us via the clinicaltrials.gov Website, traveling from

Fredericksburg, Virginia. His gout was among the most severe I had ever seen.

Due to knee involvement, he had not walked in more than four years and got about in a motorized scooter. He endured six months of placebo therapy and elected to enter the open label phase of the program.

A few months into the open label extension protocol, Mr. L walked for the first time in four years and made great progress toward becoming fully ambulatory. Striking, draining, crusted tophi on his hands resolved over a nine-month period.

These patients are representative of my experience with this drug. I do not recall participating in any clinical trial where patients were so profoundly transformed by a therapy. Their improvement was perhaps most stunning due to how low our expectations had been for severe tophaceous gout prior to pegloticase.

I appeal to the committee to support access to pegloticase for patients with treatment

failure gout, patients like those I have described and those who have come here today to tell their stories.

Their gout is severe and disabling and needs to be addressed, in spite of co-morbidities. Our well informed pegloticase patients were willing to accept risk in order to relieve certain misery.

For this orphan population of patients, pegloticase is a powerfully effective therapy. Thank you.

DR. O'NEIL: Thank you. The next speaker is Ernest Legg, who will also have five minutes. It looks like we move on to Barney Rush, five minutes.

MR. RUSH: Thank you very much. And I do not have any financial connection with the sponsor at all. My name is Barney Rush. I am very grateful to have the opportunity to speak here today in strong support of the introduction of pegloticase.

My brothers and sister and I saw what a

remarkable effect his drug had in substantially curbing the painful and disabling gout which my father had in the final years of his life. My father, Burton Rush, had led a very active life well into his 80s. He played tennis, traveled extensively with my mother, and, though overweight, he was hardy and steady on his feet.

But over the last decade of his life, he began to suffer increasingly from gout. Most noticeably, his thumb became swollen and distended, with uric acid crystals erupting through the skin as glistening small pebbles.

At first, this eruption was upsetting as a matter of vanity. It looked gross and unpleasant. But over time, the situation became more severe, very painful, and truly disabling.

He could no longer use his hand effectively for such simple tasks as buttoning his shirt. In fact, my wife took the buttons off his shirts and replaced them with Velcro strips so that he could still at least close his shirts across his chest. He also had severe gout on his

elbows and elsewhere in his arms.

After my parents moved to Gaithersburg to the Asbury Methodist retirement community in 2004, my father's gout continued to worsen and he despaired of finding any treatment that would be able to alleviate the severe symptoms.

He had one operation to remove the crystals, which worked moderately well, but the crystals grew back and the thumb became more grotesque than ever. Then my father heard of the experimental trials being run by Drs. Barf and Wolfe. Although now 88 years old and now caring for my mother, who had the onset of dementia, my father was determined to participate.

He interviewed to join the study and was very excited when he found that he was accepted. Indeed, his major concern was that he would end up with a placebo. But it was soon evident that my father did not have the placebo. Indeed, within a few weeks, we could all see the remarkable change taking place in his thumb. And within a few months, the swelling abated, the crystals shrank

and sunk back into the skin, and then disappeared.

The thumb ultimately became almost normal in size and he was able to use it again as normal. My father was ecstatic and marveled at the miracles of science. He was also very proud that he could participate in the trials and serve the cause of medicine.

He participated in the program regularly and, to the best of my knowledge, did not miss a treatment, month after month, despite having to drive a long distance to get there; nor, to our knowledge, did my father suffer any material side effects from his treatment.

Alas, my father's body was failing in other areas besides the effect of gout. He developed bad sores which broke open and he became infected with MRSA. This led to a physical collapse in January of 2007. He undertook what became a very arduous six weeks of rehabilitation, but when the staph infection re-erupted, he chose to move to hospice, where he died in March 2007, just two months before what would have been his

90th birthday.

While my father was in the hospital and rehab during those last weeks of his life, he still looked forward to finishing his treatment and felt it was important to do so, for he wanted others to benefit as he had so evidently benefitted himself.

He had no doubt that this treatment had made an enormous and positive difference in the quality of his life. And I know that if he were alive today, he would be here in this room adding his strong voice to those who are advocating the use of this remarkable medicine. Thank you.

DR. O'NEIL: Thank you. The next speaker is, I believe, Ernest Legg. Is that correct?

DR. DINWIDDIE: No.

DR. O'NEIL: No, I'm wrong?

DR. DINWIDDIE: Madam Chairperson and other dignitaries, my name is Bethel Dinwiddie.

DR. O'NEIL: Thank you.

MR. DIWNIDDIE: I am a recipient of one of those -- I had to run back here. Excuse me for

a minute -- one of those trials, the basis of the medicine that we were here talking about. Without it, I can definitely say that I wouldn't have been here. I had given up on everything about life.

I had to quit working, retired, of course. I couldn't walk and everything I did, I had to depend on someone else to help me with it. This included the fire department. I had to get them to get me out of bed and to put me in a car and, of course, take me back out of the car when I'd get back and put me back into bed.

After a while, when you're dealing with a situation like that, your friends and your relatives and everything else will soon get tired of doing it. So after a pretty good period of time, I decided that life just wasn't worth living. But I was fortunate enough to have a doctor that introduced me to this program.

As far as I was concerned, it was just a day out, out of the house. I had been poked and prodded and stuck by every known specialty that I could find and I was just progressively getting

worse. So when I got here, when I got to the program, I really had no hope. And as things went on, after my first treatment, I noticed a remarkable improvement.

So unless you have a picture which duplicated the ones I saw on the screen of how I looked, this was hands, elbows, feet, knees, everything. I couldn't walk. I was really bedridden. But after a couple of treatments, no one had to help me come back in to get a treatment.

My treatments went from 30 days, once every month, to every other week. And now, as you see, a lot of the places that showed up on that film that you had, my hands and so forth, you can't even tell they were swollen or deformed, whichever way you want to call it. That's why I guess I'll not tell the whole story, because time is running out. So thank you very much.

DR. O'NEIL: Thank you, Mr. Dinwiddie. Next, we will hear from Timothy Schwarz.

MR. SCHWARZ: Savient did pay for my room

and flight to be here today. I thought I was always the worst case of gout I had ever seen, until I've seen what I've seen today. I see that there are other cases. I mean, I have my fingers, here they are, breaking through. I haven't had a chance to have the treatment. I'm here to say what it would mean to me to have that opportunity.

I'm a single father. I've raised my son on my own since he was about two months old. This disease has cost me my career. Not only is it in my hands, but my elbow, breaking through on this elbow, my feet, my knees, and it's becoming progressively worse.

Pretty much, if I work more than two hours, I'll flare up and I'll be down for a week crippled. It's made it real hard to take care of my son. The pain, I can't exaggerate the pain enough. I had opted to do surgery to -- I had a golf ball size on my finger and my pinky, as well; probably not the right choice, seeing what I've seen today, that the tophi can be reduced, because now I have no feeling in my fingers where it, I

guess, cut on the nerves trying to get the tophi off of the knuckle.

The medicines I'm taking, colchicine, Indocin, I take prednisone 20 milligrams a day, which sounds very dangerous, after what you all had to say today. It's the only way I can seem to walk. If I don't have the prednisone, I'd be crippled. I'm very careful with my diet.

I had pretty much given up hope, like this gentleman before us. I feel like that I'm going to lose a limb soon or possibly die from this disease in a very short period of time. It's progressing that fast.

And I just am excited to -- it just gives me hope to hear what you all are talking about today. I didn't realize that there were so many people interested in finding a cure for gout, and I'm just totally excited to hear that there's an opportunity for me to live again. And I appreciate your time. Thank you.

DR. O'NEIL: Thank you, Mr. Schwarz. Next, we will hear from Lonnie Matthews.

MR. MATTHEWS: My name is Lonnie Matthews. I received financial assistance from Savient for one night's hotel room. I also wish to inform you that I own 1,000 shares of Savient stock, which I purchased after my very successful experience with the Savient drug, pegloticase.

Like many people my age, I am plagued with many health issues. Polycythemia vera was diagnosed in 1993. That condition exasperates and complicates everything else. I have fourth stage renal failure, pulmonary and cardiac problems. The gout, which I was able to control with the drug allopurinol for 30 years until my kidney failure worsened and my nephrologist advised I must get off allopurinol.

Within five days, I was suffering a gout attack more severe than any I've ever had. The only drug that was compatible with my renal condition at that time was prednisone at the rate of 60 milligrams a day for a 10-day treatment. Then I would stop the drug and within three to five days, the gout was back more excruciating

than ever.

Gout attacked my toes, feet, elbows, knees and hands, which swelled until they appeared I was wearing a baseball glove on each hand. I suffered with gout as described above for approximately one year, until was advised that Duke Medical Center was going to participate in a double-blind study on the Duke-developed drug pegloticase.

During all this time, I could not walk, was confined to bed for up to two weeks at a time, and was having to use a wheelchair. When I started this drug study, my uric acid was 22. Gout was a major factor in our leaving our two-story farmhouse to a continuous care center.

Approximately six months after the start of the treatment, I suffered a heart attack. In my opinion, this attack was in no way connected with the drug study, but was precipitated by my own stubborn ignorance. I insisted that my polycythemia vera be controlled by phlebotomy, while my hematologist insisted that I begin to

take the chemotherapy drug hydroxyurea.

My platelet count rose to 600 and shortly to one million. My arteries had no chance but to plug up and require two stents. Hydroxyurea is now a regular daily part of my treatment system. Pegloticase has changed my outlook on life and made life worth living again, in spite of all my medical problems.

In February 2009, I received my last pegloticase infusion. Since December 2007 to June 2009, I have had no gout flares, but I am incredibly fearful that I will again develop gout if I no longer have access to this drug. Thank you.

DR. O'NEIL: Thank you, Mr. Matthews. The next speaker is Jeraldene White.

MS. WHITE: My name is Jeraldene White. Savient did provide financial and travel assistance for one night, hotel room. I was diagnosed with lupus at age 45, in 1988. I'm allergic to penicillin, ampicillin, tetracycline and sulfur. In the early '90s, I underwent chemo

for blood in my urine.

In early 2000, I was treated for blood clots and a stomach ulcer. In 2003, I was alerted to problems with my uric acid due to swelling in my ankles. At that point, there was really nothing that I could use for the gout, except prednisone. Allopurinol was prescribed, but two months later, I had an allergic reaction to that.

As a result, I was really one of those people who was trying to get to any drug that could address gout. Many people will be in that same position as we move forward with bringing this drug to market. I developed tophi and they grew in my hands, all over my feet, knees, elbows. I even had some on my wrists.

This was between 2003 and 2006. There was really nothing that could be done and it was really distressing. Then I found out about the pegloticase clinical trial. In 2006, at the end of August, I received my first dose. At that point, I could not move any of my fingers, hands, joints. I could not stand.

So upon receiving the first dose, I had a major flare. I could not get to the telephone to call the -- Dr. Baraf had to have the police department break in my house twice in order to get me up to get my medicine.

Even though I was weak and had to be hospitalized, after that first dose, I began to notice slight changes in the movement in my fingers. And I told everybody about it, even though I was laying in the bed. This improvement in mobility continued through the course of the trial and today, I am able to lead an active life and all of the mobility has been restored to my joints.

I would encourage you to consider this drug. There are millions of people that suffer from gout. I never realized it until I passed out one day at work and the nurse from work came and she told me about all of the remedies of people in the building that I worked in who also had gout. I had no idea. Thank you.

DR. O'NEIL: Thank you, Ms. White. The

last speaker in the open public hearing is Ernest Legg.

MR. LEGG: Good afternoon. I'm Ernie Legg. I'll be 50 years old next month. I didn't prepare a speech or anything, but I do feel it's important to come and talk to you. I was diagnosed with gout, just a sore toe, back in 1993. They told me that it was treatable with allopurinol.

I started taking allopurinol. Not long after that, I started suffering from some pretty severe side effects, difficulty breathing. They said, "Well, you can't take allopurinol." So we just kind of -- we let it lay like that for a while. Not long after, the gout attacks started to increase a lot. They moved from the foot up into the knees. People that I worked with saw me on crutches, "Hey, what's going on?" "Well, I've got gout, can't seem to take the one medicine that helps you."

Years went by, I got worse and worse, started getting the tophi buildups everywhere. My

elbows looked like softballs, basically. There were ruptures, stuff was coming out; went from the crutches to a wheelchair, from the wheelchair to a car or scooter; had to modify my entire house. I was basically becoming crippled.

I didn't know what to do, saw a rheumatologist. A rheumatologist down in Fredericksburg, Virginia said, "If you can't take allopurinol, there's really not much I can do for you. If you find another treatment" -- you'll have to excuse me. I'm a little emotional -- "If you find another treatment that another doctor prescribes, I will be happy to carry through with that to help you come to a close office. But other than that, there's not a thing I can do for you."

Pretty much resigned to being crippled, starting to consider not being able to go to work. My wife read a magazine article about a study being conducted in Wheaton, Maryland for the treatment of gout, participate in goutstudy.com. Why not? Give it a shot.

So that was two years ago and Dr. Baraf here took me in and we started the treatments and the fact that I walked up to this microphone is a miracle of modern medicine. I am recovering at light speed. The tophi are gone. I've regained use of my hands. I got a motorcycle license, riding a motorcycle. My wife and I went out this past Sunday. The weather was beautiful here, by the way.

Life is on the upswing. Please, please, please consider approving this drug. It's helped me to regain my life and I'm sure there are millions of other people that could benefit, too. Thank you.

DR. O'NEIL: Thank you. Mr. Legg's comments make me wonder about the CNS side effects of the drug. For the non-medical people, that means the brain side effects and judgment.

The sponsor has asked for five more minutes to clarify some issues brought up during the question period.

DR. SCHWEITERMAN: Thank you very much,

Madam Chair. Yes, I'd like to bring up several different speakers in a row, to not take up much of your time, but to answer some of the issues that arose during the morning session.

Dr. White?

DR. WHITE: Thank you very much. I appreciate the opportunity. Slide up, please. There was a comment about the disposition of deaths. I just want to make sure we all are clear what we did and what happened in the clinical program.

As you recall, we adjudicated two CV deaths in this group, q2-week, and one non-CV death, one non-CV death in the q4-week group, and three, of course, some of them occurring post-study, in the placebo group. Next slide.

So just to make sure that everybody is aware, it was stated in the FDA Q-and-A that two of the cases that were late, in fact, we were due to side effects from the drug and they withdrew from the study. That is, in fact, not correct.

They were placebo patients, not active

treatment patients, who completed their study and then these events occurred outside of the window of the 30 days that normally we look at other events, because there was no censoring of death.

So to reiterate, two CV deaths in q2-weeks, the one MRSA sepsis here and one here in the placebo group, as well, a renal failure patient who declined dialysis, and one patient who died of recurrent CLL and infection, and a last case in the placebo group in which it was called multisystem failure. We do not have enough information to give a formal adjudication or diagnosis.

So this is the way I and our committee read the events occurring.

DR. PACKER: Billy, just so I understand, the two events on placebo, I'm just trying to compare apples and apples.

DR. WHITE: Okay.

DR. PACKER: If you look only at the time from randomization plus six months, that way, every one, the denominator is approximately the

same across the groups in terms of time. The two events of the deaths in placebo were four months after six months.

DR. WHITE: Yes. Yes, they were. But remember, the denominator was 43 and in the other two groups, they --

DR. PACKER: I'm sorry. I didn't mean denominator in terms of numbers. I meant in terms of time.

DR. WHITE: Right.

DR. STRAND: But I will remind you that 71 percent of the intent to treat population went into open label, but it actually represents 98 percent of the people who completed the six months treatment. So we would have had follow-up on those other subjects if they were persistent responders.

DR. PACKER: Let me see if I -- just to clarify. The two placebo deaths that are there, which occurred four months after completing the course of therapy of placebo for six months, did they occur on open label?

DR. STRAND: No.

DR. PACKER: No, okay.

DR. STRAND: They did not enter open label.

DR. PACKER: That's fine.

DR. STRAND: And of the four subjects that were lost to follow-up, there was only two that were lost to follow-up. They were in placebo. One in P q2 and one in P q4 were either protocol violation or they had not complied with the protocol.

Slide up, please. I just wanted to clarify that patients were seen every two weeks. Now, in the pegloticase q2-week group, that meant, of course, that they have active therapy infusions every two weeks. In the P q4 group, it would mean that they alternated between an active infusion and a placebo infusion every two weeks, and, in fact, there were infusion reactions that occurred in five of the pegloticase q4-week treatment group while they were receiving placebo.

Furthermore, there were also two infusion

reactions in placebo treated patients who received placebo throughout the six-month period. So we don't believe that infusion reactions, per se, were a reason for unblinding. Furthermore, there were nice responses in the patient-reported outcomes at the first evaluation, which subsequently deteriorated in the placebo subjects, but continued to improve in the active treatment group. That would be consistent with the placebo response.

Next slide. So what we wanted to, also, clarify one more time is that the in the pegloticase q2-week treatment group, 20 of the 22 subjects who had infusion reactions had them after the serum uric acid was greater than six milligrams per deciliter. So the proposed stopping rule would have prevented 91 percent of these infusion reactions; also, to remind you that this loss of serum uric acid response has occurred in every subject within the first three months of treatment.

And now I'd like to ask Dr. Lipsky to

come up. So, again, to remind you that the persistent responders in pegloticase q2-weeks, only one of those subjects had an infusion reaction. So benefit is associated with few infusion reactions, in fact, almost none, and with persistent response.

DR. LIPSKY: My name is Peter Lipsky. I've been a clinical immunologist for 38 years, which I hate to admit, and I was contracted by Savient to review all of their data related to immunogenicity. And I've done that and I must say that Savient made all of their data available to me, responded to every one of my requests, and in no way tried to interfere with my interpretations of the data.

So I have looked through all of the antibody responses and the infusion reactions and I'd like to bring up three quick points. One is that I would like to ask for a clarification from the FDA, because they presented us with a document last night looking at reactions that they felt met the criteria, clinical criteria of anaphylaxis

based upon a paper by Samson, et al, from 2006. Could we have that slide?

And you've seen this slide. And what this is is a compilation of the infusion reactions that the FDA designated by F, F on the slide, met the Samson criteria. Now, on page 4 of the document, they include data which would imply that anaphylaxis, as defined by the FDA, according to the Samson criteria, was more frequent in the q4-week group versus the q8-week -- was more frequent in the q2-week group compared to the q4-week group.

And I must say I've looked through each one of these and I cannot validate that data whatsoever. I find, in looking at this, that eight individuals in the q2 week received therapy -- received or had reactions like the Samson description, whereas seven had it in the q4, and, actually, two were receiving a dose that's not in development, q12 or four milligrams q2.

So I'd ask for clarification from the FDA

as to where these numbers came from, because, frankly, the committee has responded to the apparent imbalance showing more anaphylactic type reactions in q2, and I cannot personally validate that information.

I think more importantly than that is the fact that the Samson paper made clinical criteria meant to alert primary care providers that a set of symptoms might be anaphylaxis. They discuss in the paper that anaphylaxis is an IgE mediated mechanism and that they also -- that these clinical criteria are just alerting physicians and not documenting that there's an IgE mediated mechanism.

However, the word anaphylaxis is powerful and it means that one has a question as to whether or not there will be vascular collapse and death. So I think it's very important not to use this word as a surrogate unless actually a mechanism has been demonstrated.

In fact, if you look on the right side of this slide, you'll see that in most of these

individuals, evidence for real IgE or immune complex mediated mechanism has been explored and, in fact, the evidence from these patients that either an IgE mediated mechanism indicated by increase in tryptase, showing mass cell degranulation, or a CH60 decline showing an immune complex mechanism, is actually infrequent.

In fact, it's no more frequent in this group of individuals than in the other infusion reactions that were not categorized either by the company or by the FDA as anaphylaxis.

So I think it's very important to -- in this context, we're looking for a mechanistic understanding rather than just a clinical description. And, in fact, the number of cases that have true evidence of immune mediated mechanism is less than half of these and no more than in the individuals who don't have criteria for anaphylaxis.

But the final point, and more importantly, is that the vast majority of these reactions and the other infusion reactions occur

at a time when the decline in serum urate has been lost. So most of these people would not have received an infusion, let alone have a reaction, if the proposed stopping rules were actually followed, and I think that's a very important point.

Thank you for your attention.

DR. SCHWEITERMAN: I'll be very brief here. Slide up, please. I just wanted to respond to a general question about the use of this drug. Of course, this is a -- the benefit-risk profile for this drug, in our opinion, is extremely positive. The question had to do with the types of responders and then the possible attrition through to the use.

I call your attention just to the second bullet here that control of hyperuricemia itself, as based on the evidence, was profoundly associated with the elimination of tophi, as well as tender and swollen joints and patient reported outcomes. And in those patients who responded, unlike those that didn't, there was an excellent

safety profile that lasted throughout the course of therapy.

Next slide. This, of course, manifested in profound reductions in the tophi and other -- could I have the picture of the tophi, please?

The other tophi and other responses that occurred during therapy. Then, finally, managing the risks of therapy, as shown in this particular slide, where we are able to eliminate the infusion reactions.

It allows us, for a, I think, remarkable opportunity to actually maximize the benefits in those who are responding and persist with that response and don't experience the safety profile, as well as addressing the cardiovascular risk and the registry.

So it's a general sort of interpretation of the context by which these patients not only benefit, but that the risks are minimized. Thank you very much, Madam Chair, for the time.

DR. O'NEIL: Dr. Siegel?

DR. SIEGEL: We're in a funny situation

that the sponsor is posing a question of the FDA. We're happy to answer questions from the advisory committee and if someone on the advisory committee wanted to pose a question, we'd be happy to. If you want us to just answer those questions, I guess we could do that, too.

What would you like us to do?

DR. O'NEIL: I think it would probably be helpful to resolve those questions. Thank you.

DR. SIEGEL: Okay. I'll start and then I'll need to bring in some other people to address a few of the specific questions that Dr. Lipsky brought up.

So the broad question is why did we apply the NIH/FAAN criteria to characterize patients with anaphylaxis, and there are a number of reasons. One is that anaphylaxis doesn't have a uniform definition. As Dr. Lipsky mentioned, it's often said to be associated with a particular constellation of signs and symptoms in association with IgE antibodies.

But it's also clear that not all cases of

allergic reactions are mediated by IgE antibodies. So we wanted to use a definition that wouldn't rely on a particular mechanism. For clinicians, what's important is what fraction of patients have the constellation of signs and symptoms characteristic of anaphylaxis.

There are a couple of other reasons why relying on IgE antibodies is not necessarily the optimal method here. One is that you don't always have an assay that's sensitive for picking up IgE antibodies to the allergen. And the other concern is that sometimes laboratory measures aren't available and then how do you characterize an event.

So we thought it would be worthwhile to use a single standard definition for anaphylaxis based on the clinical criteria and thought it would be worthwhile to see what fraction of patients in the different treatment arms met those criteria.

Nonetheless, we recognize that not all these cases may be IgE mediated and the committee

will, of course, need to take that into account in evaluating the data and the significance of the data.

Dr. Lipsky brought up two specific concerns. One was if we could justify how we got a higher rate of anaphylaxis in the q2 than the q4 and -- what was the other specific question?

I'd like to ask Dr. Lim to address that question.

DR. LIM: Susan Lim. I'm the allergy consultant for the FDA. So getting to this question about different anaphylactic rates depending on the dosing regimen, I wouldn't make too much about that difference. I think the reason for showing that was because when we looked at infusion reactions overall, there seemed to be a higher frequency of those events occurring in the q4-week regimen as opposed to the q2-week.

And so we tried to break down the anaphylaxis to see if it followed that same pattern and it went the opposite way. But again, the numbers are small. So I wouldn't make much of

it. That wasn't our intention for showing those frequencies.

Then just to add to what we were talking about in terms of the usefulness of having a mechanism, as most people who are familiar with drug allergy, it's very difficult to establish a mechanism for an allergic reaction. And so if we were to wait to have the technology to confirm that there was an IgE mediated mechanism involved, then it would be very hard to call anything anaphylaxis. And I think if you go back to the original Samson paper in 2006, a large part of that discussion focuses on how understanding the specific mechanism is not critical when you are dealing with the patient in the clinical setting.

So we've used this criteria to look at the safety database for a pegloticase, as well as for some other drug programs, and the point is to have a uniform definition. I think if we lump everything within the -- under the umbrella term of infusion reactions, that doesn't do much service to the health care providers who are going

to be trying to understand what is the risk profile for the drug.

DR. O'NEIL: Thank you. Dr. Siegel, you're done? Okay.

Dr. Packer?

DR. PACKER: The one thing about the anaphylaxis reactions is the feeling of the sponsor that if the serum uric acid goes to greater than six, that is a non-responder and the patient more likely to get infusion reactions if they continue to get the drug.

Can you put up slide number 46 from your original presentation? Just to make sure, this is the slide that you showed that showed the urate mean uric acids -- it's plasma here, but it doesn't matter -- in the non-responder group, getting every two-week infusion.

So we're looking at the bottom blue/green line.

DR. STRAND: That's correct.

DR. PACKER: Can you just clarify when -- at what point in time do you think after the

infusions are started that someone ought to measure uric acid and make a decision about continuing or not continuing?

DR. STRAND: We recommend that you get a serum uric acid prior to every infusion.

DR. PACKER: Okay.

DR. STRAND: And that you do that for the first three months, which means through week 12.

DR. PACKER: Okay. So if I were a rheumatologist and I apologized to all rheumatologists for making that proposition, I would, at week -- in the non-responders, at week three, I would -- and tell me if I'm interpreting it correctly -- I would call most people responders.

DR. STRAND: Yes, you would.

DR. PACKER: Okay. And, in fact, even at week 12, I would call half the people -- I assume those are means. Are those means?

DR. STRAND: They are means.

DR. PACKER: So half the people that are, quote, non-responders would have a uric acid less

think six.

DR. STRAND: Yes. But I think what we need to do is also look at the persistent responders, which is in a previous slide, because you'll see that, in fact, people don't even go up to uric acid levels of four or even approach six.

DR. PACKER: That's exactly my point. If you look at the slide before this --

DR. STRAND: It was very difficult to look at -- yes, we can go to the -- but remember, we're looking at means and the individual subjects show it very, very clearly and, again, look at the P q2 means, where they are all -- all of them are below two.

DR. PACKER: And you're exactly -- you understand my question. Every responder here is below two.

DR. STRAND: Yes.

DR. PACKER: If you go to the next slide, which is the transient responder --

DR. STRAND: No, not every responder is below two. Go back, please.

DR. PACKER: Go back.

DR. STRAND: The mean is two or below two. That certainly means that half of them are above that.

DR. PACKER: Okay. Go to the next slide.

DR. STINE: It would still be less in that case because it's skewed.

DR. STRAND: Yes, it is skewed, also, that's for sure.

DR. PACKER: I totally understand. But next slide. What I'm trying to understand is why are you proposing a cutoff of six instead of, say, a cutoff of four.

DR. STRAND: Because we know that if you have a uric acid level that is six or below, then you will be mobilizing the body urate stores and you will still be responding. And you may have heard, the people who entered this study had mean levels of 10 or above, but we just know of one subject who was 22.

So as long as there's clinical benefit, which is sustained and believed to be occurring at

levels of six or below --

DR. PACKER: No, no, no. First of all, you haven't established that there is clinical benefit at six or below.

DR. STRAND: Well, we've looked at the other ones, as well. We looked at lower cutoffs. We get the same effect of basically identifying the transient versus the persistent responders, whether it's four, five or six.

DR. PACKER: My concern is that -- I mean, these data, at least to me, suggest that if you have someone who comes in at 5.8 -- I'm just making up that number.

DR. STRAND: Okay.

DR. PACKER: And that they were previously at one --

DR. O'NEIL: I think, Dr. Packer, you've made your point.

DR. STRAND: Dr. Packer? Just one more quick point, if I may, Madam Chairman. If you notice here, in these folks that are losing their response, look how rapidly these means climb.

These responses are lost immediately. I mean, they are lost between the two-week infusion times.

DR. PACKER: Just to clarify. If someone came in with a uric acid of one after the first infusion and went up to a uric acid of 5.8, would you consider them to be a non-responder?

DR. STRAND: Yes.

DR. PACKER: Then we have to change our threshold for what's a responder and what's a non-responder.

DR. O'NEIL: I think, Dr. Packer, that's probably something that we will get to further in the discussion. But let's get on to our discussion, please. We have been asked by the FDA, as a committee, to discuss several issues. First and foremost is the safety of pegloticase.

The populations enrolled in the two Phase 3 trials of pegloticase had a high prevalence of cardiovascular disease and risk factors for cardiovascular disease, as does the intended patient population for this drug.

A greater proportion of subjects

randomized to pegloticase had significant cardiac adverse events, as shown in tables 24 through 26 in the FDA briefing document, but the absolute number of events was quite small, and there were a variety of different types of cardiovascular events.

This is particularly difficult to interpret, because randomization was four individuals to pegloticase for each one on control. We have been asked to discuss whether the data generated by the two Phase 3 clinical trials suggest that pegloticase indeed increases cardiovascular risk. And to do that, I would like to go around the room and we're going to start with Dr. Neogi, if you have any questions or comments, and then pass the mic around.

DR. NEOGI: I think there are a number of issues raised by the safety signal in this study. One of the concerns I think is the assessment of the potential adverse events. The FDA-sponsored cardiovascular assessment indicated one of the concerns was that there was not always a

protocolized or standardized assessment of the non-serious adverse events.

So I think that raises issues of interpretability of whether or not there is an increased cardiovascular signal with pegloticase. But I think the fact that these patients, the persons enrolled had a significant number of cardiovascular co-morbidities and evidence of coronary artery disease indicates that we should expect some level of events and with so few in the placebo arm, I think it's very difficult to determine whether or not it's an expected rate or a higher than expected rate.

DR. CLEGG: As others have said, the numbers are small and we would expect to see some incidence of events. I think I've been struggling with what my colleagues have also discussed, and that is the playing field has changed a little bit since these studies were developed.

So we need further discussion on balancing this potential signal with what can be done to now optimizes uric acid levels in

patients. And I'm going to be interested in the agency's discussion about how strict a registry can be developed, because if we could develop a registry, a mandatory registry, that would basically compel optimization of uric acid before this agent is considered, I think this agent has the potential to improve lives that otherwise can't be addressed with current therapies.

MS. ARONSON: While I'm very much compelled by the patient testimony, I do have a concern about the co-morbidities. The vulnerability of a patient population, particularly in light of their medication load, which, before the protocol, was between 15 -- an average of 15 medications alone that these patients were taking.

So that, and then the load, and then trying to decipher -- there were 15 hospitalizations for serious adverse events, trying to decipher the protocol versus the patient population indication.

DR. BUCKLEY: Limiting myself to the

comments about the increased cardiovascular risks, I think the sample size is inadequate to answer it.

DR. STINE: I've already expressed my concern about the sample size and I think that's just going to be a difficult part of this whole study to try to appreciate, and especially in the absence of any sort of mechanism that you could sort of point your finger at and say, "See, this is what's happening."

I think this is going to be a very difficult issue to resolve and we have to use judgment in this particular case, because the statistical evidence is going to be uncertain.

DR. MIKULS: I think had I had a clear answer to your question, you might have hired me as your consultant earlier. But clearly, the sample size is an issue. I don't think anyone would argue that.

It's tough when you're down to three cases and you're trying to decide on that. I had asked earlier about potential temporal

associations with acute flares, with my idea being -- or a hypothesis being potentially that you could potentially have more cardiac problems because of efficacy.

In other words, if you have more flares, that's an extremely painful condition, we've heard testimony to that. It drives catecholamines. It increases -- potentially could increase cardiac risk during an acute flare.

I'm mentioning this because I would propose that if a safety registry comes together, to look at this question, that we really look at those kind of questions, are there temporal -- and it's a very difficult thing to capture, I understand. Are there associations with bolus steroids that are being used? Are there associations with increase in non-steroidal use? This is a very, very vulnerable patient population and so I would just make those recommendation to that end.

DR. O'NEIL: I think that particularly in view of the fact that this is a very difficult

population -- or I think my first kind of flippant comment is that perhaps we should be trying the placebo as a cardiovascular protective drug in this high risk population, because they seem to do better, but for very unclear reasons.

But I think that Dr. Mikuls' point is very well taken, particularly in view of the known cardiovascular risks associated with on-steroidal anti-inflammatory drugs. And I do suspect that a lot of people are using such over-the-counter NSAIDs and perhaps forgetting to enter them on their drug logs, and that may, indeed, be sufficient to double their risk, which is already quite high, for a thromboembolic event.

So I think it's because of the limits of the size of the population that is targeted for this drug, because of the difficulties with this population and the very high number of risk factors, it's going to be very hard a priori to get the data that we really need. Therefore, we are going to have to discuss how best to get the data if this drug is improved afterward.

DR. OLSEN: I don't really find it very overwhelmingly convincing that there's an increase in cardiovascular risk and I, along the lines of what Dr. Mikuls was just suggesting, I was thinking that there are risks due to the infusion reactions, because you read about the infusion reactors, they got tachycardia, their blood pressure went up, and if you already had an underlying heart condition, it would seem like that would put you at risk for another event, which is exactly what happened in one of the cases.

The other thing that struck me is that there are so many different kinds of heart problems that were reported, it's hard to develop a unifying hypothesis of what might be related to the treatment. So because of those -- if the design now going forward would result in fewer infusion reactions and better control of the flares, then maybe this problem would be less of a problem.

DR. NELSON: I actually have kind of

mixed feelings about it. On the one hand, it's pretty clear that there is a signal, I think, given a somewhat disparate signal, but cardiovascular being the link between all the different events that are going on.

I think what troubles me about is what's already been mentioned, which is kind of the biological plausibility issue when you try to kind of create causality. And a mechanism would be nice if we could somehow try to figure out what it is that would potentially be causing this, and maybe there's a chicken-and-egg thing here.

If we could figure out what it is that's causing it, maybe we could figure out what's causing it, or vice versa. But I do think that the numbers are there. I mean, they are small numbers and there's no question about that. So it's hard to really do any statistics on it to say it's real or not, but it's something that I think we must look at it and we must try to figure out.

I also think the other thing that troubles me a little bit is the fact that -- and

this is just the nature or research, I think -- is that we're looking at this in a fairly pure environment, not necessarily a real world environment. And when this gets out and we start looking at different patients and different combinations of drugs and dosing regimens perhaps and other things, I think all bets are off.

So really ought to have a pretty good handle at this point on what the real risk is at least in the defined population and hopefully be able to make some predictions about what's going to happen once it gets out.

DR. FURBERG: I find the cardiovascular data inconclusive. I think what we need is a better designed registry with a truly independent oversight committee, not the sponsor appointed oversight committee.

DR. WEISMAN: I think it could have been foreseen with the design of the study, when orphan drug status was applied, that the numbers were going to be small in a population where the background rate of cardiovascular disease was

going to be high.

So what do we do?

And the other issue that's interesting to me is the fact that with these huge swings in uric acid levels, that, in fact, there may be competing mechanism for heart disease either causing it or perhaps preventing it with these kinds of swings in uric acid levels, because some of the mechanisms can go in opposite directions, which I find really intriguing.

So what's the answer? The answer, I think, is that this requires a mandatory safety registry for all patients going on this drug. I think it will give us the most opportunity to learn something going forward for the next time.

And number two, I think the infusion reaction issue can be reasonably taken care of. We know as much as we need to know about that. In spite of the nitpicking over some numbers, that can be worked out. And I think there's a definite unmet need for this drug. So those are the three comments that I want to make. So I think we've

got a reasonable view of this.

DR. WILLIAMS: The question is: do the data suggest a cardiovascular risk? And I think that is yes. Does it demonstrate a risk? No, because of the data, the paucity of data that we have. As I looked at the vignettes that were sent to us, but not presented, of the individuals who had serious cardiovascular reactions, none of them seemed to be very surprising.

However, I'd have been much more comfortable if they had been spread over all three treatment groups, but we saw very few of them in the placebo group. So I do think that we need further monitoring and I think a registry would meet that need.

DR. PACKER: I'm sitting here scratching my head because there are so many people who say that you can't interpret the cardiovascular side effect profile unless you had a mechanism. As most of you know, most mechanisms both efficacy and safety are fabricated. We make them up after the fact and we make them up after we know that

there is, in fact, an effect, either a beneficial one or a detrimental one.

We don't have any clue about mechanisms even for effects that we know convincingly exist, either favorable or unfavorable. But the physicians are unbelievably creative coming up with mechanisms. If you wanted to come up with a mechanism for why this drug would increase cardiovascular risk, we've got data with allopurinol.

Observational data shows that it increases cardiovascular risk. We have a controlled clinical trial with oxypurinol, also with xanthine oxidase inhibitor, which shows that it increases cardiovascular risk and heart failure. We had an advisory committee for febuxostat based on concerns that it increased cardiovascular risk, and we have the same questions here.

Clearly, uric acid -- how uric acid must be protective for cardiovascular risk, and anything that lowers uric acid must increase

cardiovascular risk. Now, please understand, I'm not being serious, but the data are certainly consistent with a protective effective uric acid and that anything that lowers uric acid -- we have four different agents that lower uric acid -- increases cardiovascular risk. Sounds like a great hypothesis.

So although we all would love to know what the mechanism is, if someone were to propose it, you wouldn't be any smarter. You just wouldn't know. What we do know is that -- I went through all of the cardiovascular events and Billy will -- I didn't go through it blindly, but you'll be happy to know I got one more event than you did.

It doesn't matter. That's the whole point. I've got eight events on active therapy, zero events on pc. It's a four times as much exposure on active therapy than on placebo. One or two events in the placebo group makes it entirely neutral. I have no way of interpreting this imbalance.

Is there an imbalance? Yes. Does it mean anything? I don't know how anyone would know whether it means anything or not. The thing that's really sad is I don't think a registry is going to answer that question, because these patients had enormous cardiovascular risk factors.

And to be able to pick up a signal that is statistically interpretable and clinically interpretable when you've got patients being treated with this drug and patients not being treated with the drug and you're trying to adjust for the confounders as to why some people are being treated and some people are not, good luck, because -- would I oppose a registry? I wouldn't.

But please don't think that after five years of entering patients in the registry, we're going to know anymore about the cardiovascular profile of this drug.

DR. KAUL: The sparsity of the data, particularly the zero events in both the placebo arm confound the apportioning of risk. And so if you look at the confidence intervals, they're

rather broad, consistent with either an increased or decreased risk compared to placebo.

By my count, it's either six versus zero, APTC major events or 21 total events compare to zero; by FDA account, it's eight versus one. The one in the placebo arm was due to a so-called troponin leak of unclear clinical relevance.

So no matter which way you look at it, the data are inconclusive. And so what do we do in such a situation? Now, we heard from the sponsor, and I think they made a compelling argument, that there is an unmet need. The efficacy is indisputable.

So in such situations, what I try to do is find out a way of minimizing the exposure to risk. And how do we do that? Restrict the patient population. Given the availability of the new kid on the block, I think one way we can do that is by redefining what treatment failure gout means.

Perhaps offer this therapy only to individuals who have failed a therapeutic response

to febuxostat. And by estimate, probably about 40 to 50 percent of the so-called 50,000 target population might be redefined as treatment failure gout.

I agree with Dr. Packer that mandating a safety registry trial is probably unlikely to provide us with the answer. It's logistically impossible to do that. So the only way we can sort of minimize the exposure is to restrict the patient population further. Thank you.

DR. ROSING: I don't have anything constructive to add to the discussion at this point.

DR. BURLINGTON: When we were faced with an apparent numeric imbalance in the events lumped under the rubric of cardiovascular events and asked, without a statistical difference between the groups, is there something to worry about here, and in such a case, the first thing you need to do is look and say, "Well, was this potential signal generated by some logical and coherent grouping of events."

And if you look at FDA's table 26 in their background, by their count, four of the events were not thrombotic related or not apparently thrombotic related. Two of them were heart failure and two of them were apparently primary arrhythmia events.

So it's not clear that we pass that first test. If we looked at only the ones that FDA attributed to an ischemia or thrombotic ischemia cause, the we end up with an almost perfect balance, so four versus one in 169 versus 43 patients.

And then if we could pass, do we have a logical grouping to create the signal, we then would say, "Well, if we have a mechanistic explanation." For all Dr. Packer's heartfelt agnosticism about mechanisms, it is one of the ways we look at events and say is there something really to worry about here, and we don't have one.

And so I find it very hard to get overly exercised about this imbalance at this point, but that doesn't mean we shouldn't be vigilant and

look and see if there's something there in a larger population.

DR. O'NEIL: Thank you, panel. I think to summarize, most do not find that the evidence is overwhelming and, certainly, the statistics do not tell us that that is the case, that this drug causes cardiovascular risk.

But we all seem to share a concern that this drug will be used in a population at very high cardiovascular risk baseline and that there may indeed be a real signal there that the numbers are too small to demonstrate.

The discussion further broached on many of the issues about what we might gain from a registry, but more likely, what we won't gain from a registry. And I don't think any of us have been able to provide anything very convincing about whether that would work or not.

But I believe later on, you ask us to think about how best to do that. So we will save the discussion for later.

And let me ask the FDA if we have

adequately addressed that question, as best as one can with statistics, with confidence intervals bigger than this room.

DR. SIEGEL: Yes, we think there's been a good discussion. Thank you.

DR. O'NEIL: Thank you. I'm getting my papers shuffled around here. I'm sorry. The next topic we are asked to discuss is the efficacy, safety and overall clinical utility of pegloticase in the treatment of refractory chronic gout. And for that, why don't we start with Dr. Weisman?

DR. WEISMAN: The answer is yes. I think the data is adequate to indicate that there is definite clinical utility and I think the safety issue involving infusion reactions I think could be managed and they have managed it. So I see a yes answer to this question.

DR. WILLIAMS: I think the safety has been clearly demonstrated. I would think that in use of its efficacy, it would not only be used in patients who did not respond to either allopurinol or febuxostat, but could also be used in patients

where tophi were a particular problem.

And I can think of two of my patients who have severe tophaceous gout, allergic to allopurinol, draining tophi, renal insufficiency, failed tolerance testing. And on febuxostat, their tophi will stop draining, but they still are there, and I can see a short-term use of this drug and then going on to controlling their gout.

So I think that there are other areas where this could be used in efficacy, as well. We have other drugs that we use that are given by infusion that get infusion reactions, including those that would meet the criteria for anaphylaxis, and we are aware of those and that can be dealt with.

DR. PACKER: Before commenting, can I just ask a question? What is the indication being pursued? What is the -- because if I remember correctly, the orphan drug application was to control the clinical consequences of refractory hyperuricemia.

We have heard the term refractory,

treatment refractory gout or treatment resistant gouts. So what I really would like to know, and I looked for it in the briefing document, I could not find a proposed indication. So it's a little bit hard to know what we're voting yes on or no on.

DR. O'NEIL: We are discussing rather than voting at the moment.

DR. PACKER: Here's the reason for asking the question. Normally one -- yes?

DR. SIEGEL: So we obviously don't have a fully thought out position on that right now, but I can share a couple of things that might be helpful in your consideration. So breaking it down first to the potential benefit in the patient population.

The patient population is pretty clear. It's treatment failure, patients refractory to conventional treatment. What would need to be worked out is if this would be indicated for treatment of hyperuricemia in those patients or it would be something beyond that.

DR. PACKER: The reason I'm asking the question is that the original wording was to control the clinical consequences of refractory hyperuricemia. That would mean that the indication for this drug would be the reduction of tophi, swelling, tender joints, all of the symptomatic and crippling manifestations of chronic gout, all of which I think are terribly important, but represent secondary endpoints in these trials.

Normally, and I want to be a stickler here, one grants an indication on the primary and, where appropriate, on the secondaries. So if one way of resolving that or -- I don't if it's even a dilemma -- would be to say it's indicated for the treatment -- management of treatment refractory gout or however you want to say that, for the control of hyperuricemia and the reduction of the clinical manifestations of -- however.

The goal isn't to wordsmith, but it is important to try to understand that if this is a drug which is the first drug ever to show complete

resolution of tophi and other things, the sponsor ought to get credit for that in the indication section and that should be used to define a population for clinical use.

DR. O'NEIL: Dr. Rappaport?

DR. RAPPAPORT: With all due respect, what we'd like you to discuss is the efficacy, safety and overall clinical utility of the drug in the treatment of severe, chronic, however you want to define it, but discuss the clinical situation.

Then we have a pretty good track record of figuring out how to -- what should go in the label and what should be an indication and what should be a claim.

DR. PACKER: Then I apologize. Then the one thing I would say, though, is that I am concerned about what the sponsor is proposing as a cutoff for uric acid between the responder and non-responder, and we can talk about that later.

DR. O'NEIL: Yes, that's clear. One quick comment from Dr. Williams.

DR. WILLIAMS: I didn't want to give the

impression I thought that every tophus needed to be treated with this drug, because some tophi are just nuisances. But there are tophi that can be part of the disabling process or lead to loss of digits because of infection and so forth.

And I think that those large tophi, this would be a -- we don't have drugs that rapidly decrease tophi and that would be one thing. And I think that the definition of treatment refractory gout is wide enough that I could use it for whatever I want to.

DR. O'NEIL: I'm going to ask the panel to try to stay focused on the question at hand, which is the efficacy, safety and overall clinical utility of the drug. Dr. Kaul?

DR. KAUL: I think the overall efficacy has been established quite convincingly, although there are some lingering issues with what is the optimal dosing strategy. Is it q2-weeks or q4-weeks? And I did not hear a clear-cut distinction in the answers from the sponsors, as well as the FDA.

As regards to the safety, I still maintain that the most effective strategy to mitigate risk is to minimize the patient population that is going to be exposed to this drug.

DR. RAPPAPORT: Could you expand on that a little bit, how you would see that happening?

DR. KAUL: Well, I think if we already have an alternative therapy which, in the FDA's judgment, has a desirable benefit-risk profile, I think we ought to try that first before arriving at this very efficacious therapy.

DR. ROSING: I also believe that the sponsor has demonstrated that they are providing us with a drug that is efficacious in the group that they have very well described by their inclusions and exclusions.

My concern is that when the drug is released, just as I think I heard, these inclusion and exclusions may not be followed as closely as they should and I think that's where we're going to get into problems. But I think in the patient

group described, efficacy, as well as safety, with the guidelines discussed and clinical utility has been demonstrated.

DR. BURLINGTON: I think there's clear and unequivocal evidence that the drug works on the primary endpoint of uric acid. It seems to work rather well on tophi, at least in a subset of patients who remain responsive to it and don't have an antibody response. And I think that further evidence of the efficacy is that after a first couple months of increased flares, the flares go down, as well. And the effect size is attested to by the relatively small study size in order to determine the effectiveness.

In terms of safety, we've talked about cardiovascular risk already. The other major issue is these infusion reactions and whether they portend really serious outcomes for the patient. I have no doubt that eventually some patient will have a terrible outcome, but most of them were, in fact, relatively mild and responded to treatment.

Overall, it looks like it's clinically

efficacious in carefully selected patients.

DR. O'NEIL: Dr. Neogi?

DR. NEOGI: I agree with the previous comments about the efficacy. I think the q2-weeks was shown to have greater efficacy than the q4-weeks. And I think, theoretically, with the graph showing the bouncing around of the serum uric acid with the q4- weeks, that it makes sense to have the q2-weeks, where you have a more stable serum uric acid.

And the one thing that we haven't discussed is the fact that the serum uric acid actually goes very low. This is lower than any other treatment that we've seen. There are some long-term potential adverse effects that we will not pick up in a six-month or 18-month follow-up.

There is some evidence that very low uric acid levels have an adverse effect on neurologic outcomes on incidents of Parkinson's, poor stroke recovery, et cetera. So I think when we get to talking about the registries, it's not just about the immediate cardiovascular signals, but also

potential long-term effects.

The other issue about efficacy that we don't have any data for right now is after 12 months of treatment, if a person can't take febuxostat for maintenance, what would happen then? And I know that there was some data presented that seven participants were re-treated with pegloticase, but we would need more information about what happens after stopping the pegloticase for these patients and redevelopment of their gout.

In terms of safety, I think we've discussed the issues of infusion reactions and I think most rheumatologists have dealt with infusion reactions with other biologic agents and I think the plan that the sponsor has provided seems reasonable in terms of being able to potentially identify individuals, and I think eventually we'll be able to find other biomarkers to predict the occurrence of these high antibodies.

I think the overall clinical utility is

dependent on what we define as treatment refractory gout. I think that, as other people have said, the definition for treatment refractory gout is now going to change with the availability of febuxostat. So we may be seeing a smaller and smaller patient population for which this drug will be of value.

But I think there is an unmet need and even if it is a small population, it is a population that does need this drug because there's nothing else that they have available to them.

DR. CLEGG: I agree with what others have said about efficacy having been demonstrated and share the safety concerns. I don't share -- I'm not as pessimistic about the ability that other agents have to develop hypouricemia, allopurinol and febuxostat, and I view it at the time that we can educate our colleagues about optimizing those therapies and, thus, as Dr. Kaul has pointed out, limiting the population that would need exposure to this.

MS. ARONSON: Well, I've referenced the concern about the prednisone use and sort of the long-term protocol effects on patients, what happens after they stop. Another concern I have relates to the deaths and the medication load that I mentioned was for patients who had died. And most of the patients, except for one, were 60 years old and above.

So I'm just wondering about that population. I was primary caregiver to my mom, who had a lot of these co-morbidities and after a year of hospitalizations with the hydrocortisone IV and then the prednisone, she said, "Get me hospice," that it was just so challenging for her as an elderly person.

DR. BUCKLEY: I agree that this is a very effective drug in short-term control, for a year control, and I think that's an important thing. I think the safety, I'm convinced, can be improved by sort of choosing the right patients and watching the right signals for modifying or stopping treatment.

I'm concerned about two things. I'm concerned about this drug -- although short-term is important, this is a chronic disease and it's unclear to us what the role of this drug is, whether it'll be recurrently used and what the side effects of that will be or its role in addition to other mediations that are available.

My other concern is that I think that this drug may go into much wider use than we think it will be and that rheumatologists or nephrologists will have their own definition of what they think is the best treatment for a patient and that by trying to define treatment failure gout, we think we can control that.

But in the end, I think it's going to be a judgment that's made privately in an office. So we have to be prepared for this, not to be in very limited use, but potentially or at least in some areas, if people have infusion centers or have a patient who has trouble with compliance, may not meet all the criteria, but is just someone, given the milieu of some dementia and 12 other meds

they're taking, isn't taking their medicine, this may have a much broader market.

I think both the long-term use needs to be more carefully thought out and the fact that the market -- that we may not be able to control the patient population I think needs to be thought out, as well.

DR. STINE: I generally agree with the sense of the committee that the drug has shown itself to be highly efficacious, albeit there's this concern that maybe it's too good to be true or better than people need it to be.

I think that we all agree that there are issues about safety, but they're not issues that we're going to be able to resolve here today and there are going to be concerns about that, particularly as, sort of the speak, the genie gets out of the bottle and the drug starts to see much wider use than what you see in a clinical trial, and I think that's always a concern with these new medications that the word is going to be out that there is this miracle thing that you can use to

treat this and there's going to be demand from patients that maybe aren't the ones that meet the protocols shown here.

But when they find out that there is this sort of treatment available where it hasn't been, there's going to be a lot of increased scope of use. And how you try to watch that and control that, I'm not really sure. And I don't know if putting it on the indication label is enough to do that.

DR. MIKULS: So I do believe there is an unmet need for an agent like pegloticase. Clearly, those of us who take care of these patients have seen these patients, and so that's good. Is the drug efficacious? It certainly appears to be. I think the most exciting data that's presented is that with tophaceous gout. We haven't talked a lot about resolution of tophi previously.

In terms of safety, the cardiovascular risks I think we discussed. I think we talked about the need for maybe surveillance there. The

infusion reactions, which I believe are mitigated with the plan the sponsor has put forward, at least in part, I know it's been said several times, but I'd also echo, as a rheumatologist and someone who has done research in quality of care in gout, I am very concerned about suboptimal care that's out there.

And so I am concerned that this drug, as has been hinted at, will be used in patients that it's not appropriate for. And I could go on, but I'll just cut it at that.

DR. O'NEIL: My feeling is that this is a drug that the sponsors have very nicely documented efficacy both for lowering uric acid and for controlling a number of the consequences of hyperuricemia.

So I think the question of efficacy is not a very big question whatsoever at this point. I think just as a response somewhat to how one can assure that the drug is used appropriately, unfortunately, there really isn't a whole lot of way to do that, except that the marketplace will

do some of this.

Third-party payers will not allow this drug, which I am sure is not going to be as inexpensive as allopurinol, to be used unless there, indeed, a demonstration of a certain number of criteria, and I'm sure it will have to be prescribed by a physician who has some expertise in treating gout, and, also, will have to be prescribed, at least at first, by -- to a patient who has failed and has demonstrated to the insurance company's satisfaction that less expensive and potentially less toxic agents have not -- have been adequately used.

DR. OLSEN: I am most impressed with the efficacy in treatment of tophi, which we have learned today much more than just cosmetic deformities, but can cause significant impairment in health.

I'm less concerned about safety, because I agree with the idea that if it's given to the appropriate population, the safety issues are worth the risks because of the benefits.

I would want to remind the sponsors and the FDA that it would be nice to have materials for patients to be educated not only about the drug, but about gout, because that's part of our whole problem in treating patients who may request therapies that aren't indicated. They have poor understanding of really what the big picture is and there are there challenges there.

In the population I treat, they include not having English as their first language and not having a degree of education that always understands what it is we're telling them. So I think that should become a component of what is going to be put in place going forward that we can all -- we're learning about the natural history of gout.

We've taught for years that if we lower uric acid, the tophi would go away, but I don't know that I ever actually believed that, although I taught that, and now we actually can see that we've proved that.

So we will learn further about whether --

maybe if you debulk all of this, you can maintain it on the other drugs that we have, and I think we'll have to collect that information as we go further with this.

DR. NELSON: I'm not sure there's very much to say at this point. I do think that the efficacy itself, per se, is clear. The safety is questionable, as we've already discussed. The overall clinical value, I think that becomes a risk-benefit analysis and we're missing one part of that equation.

So I'm not exactly sure how to decide just at this point, without more information, whether or not the value is there, and I think that more information is still needed.

DR. FURBERG: Regarding population, I'm okay with that. I'm okay with efficacy. For safety and utility, my answer is it depends. I'm unwilling to sign a blank check. So I'm leaning toward conditional approval.

So approval will depend on the wording of the labeling, particularly the sections on

contraindications, precautions, warnings, et cetera, carefully worded. Approval would also depend on the decision regarding a medication guide which the sponsor was in favor of. I like that. I'd like to see a well written, balanced medication guide.

Approval would also depend on what we decide about additional studies, the post-marketing studies that we're going to address a little bit later this morning. And, finally, the remaining worry I have is long-term safety.

Since we don't know the mechanism of action, as Milton pointed out, what's behind all the adverse effects. How can we say that we have six-month data that we know that the drug is safe? It may take longer for adverse effects to show up. And we need to have much more information, controlled information regarding the long-term effect of the drug.

DR. O'NEIL: Thank you for the -- yes, Dr. Rappaport.

DR. RAPPAPORT: I'd like to make sure

that everybody understands what our authorities are now, because things have changed a lot in the last couple of years with the passage of the Food, Drug and -- the FDA Amendments Act a couple of years ago.

We now have the authority to mandate certain safety interventions and risk management strategies. Those include mandating studies in the post-marketing period. We can now require them and they are enforceable. It is an enforceable requirement.

There are certain limitations on what those studies can be. There has to be a comparator, et cetera, and it has to be around, say, formulated primarily around safety. We can also mandate a REMS, a risk evaluation and mitigation strategy, and a REMS can include a number of different features.

One is a med guide. You can have what's called a med guide only REMS, but you can also have REMS that include other features. And the elements to assure safe use part of REMS are the

things that really restrict is use.

So if we were to go to use the elements to assure safe use, we could actually implement a prescriber registry, a dispenser registry and a patient registry, any or all of those, as are deemed appropriate for the drug in question, to restrict is use to the proper population.

The onus then falls on the NDA holder, the sponsor, to ensure that whatever the restrictions are are actually occurring and that people are not receiving off-label drug. Again, it's enforceable, there are fines and there is the potential for making a drug -- of finding the drug to be -- to take it off the market, essentially, if we have to.

So these new authorities do have teeth. We can actually do something and we can actually restrict a drug. It's meant not to be too onerous on the system and we do have to keep that in mind as we go through this, but if -- I just want you to all understand that so that when you're making decisions on how to vote on this, that we do have

those kinds of authorities and we could implement them if we see that that's what's needed.

DR. FURBERG: Dr. Rappaport, I didn't mean to question your authority and so on. I thought possibly that you wanted to hear the views of the members of the panel, who have gone through the data and we may have some thoughts that you possibly could benefit from.

DR. RAPPAPORT: Oh, no, absolutely. I wasn't -- that wasn't directly to you. It was because I heard from a lot of people that you think that maybe this should be restricted to a particular group of patients, a very limited group of patients.

But I also heard that there was a sense that maybe it was going to get out of that population into the general population no matter what we put in the label. And I think we have the means these days to prevent that from happening.

DR. FURBERG: I like the idea, personally, about the risk management strategy, and review those options. I think they would be

very useful and make me very, very comfortable.

DR. O'NEIL: Thank you. That does make our deliberations in the next section a lot clearer. We have one more comment by Dr. Buckley, I think.

DR. BUCKLEY: I guess it's a question. So just to understand the options, if we have questions about the long-term safety and the long-term utility and broader use, one of the options today would be a limited approval in a certain population with the suggestion for ongoing studies that might address safety issues or other issues; not just registry, but ongoing placebo-controlled --

DR. RAPPAPORT: Yes, I wouldn't call it a limited approval. It's an approval. The drug is approved, but you just restrict the population to a very specific group of people and we can determine who that should be.

And, yes, you could include -- you could recommend to us that we include post-marketing study requirements and suggest to us what those

might be. Those are the kinds of questions we're -- those are the kinds of answers we're hoping to hear from you today.

DR. O'NEIL: All right. Thank you. If there is no further discussion on this question, we will now begin the voting process. But first, let me review the voting process for everyone.

We will be using the electronic voting system for this meeting. You each have three voting buttons on your microphone, "yes," "no," and "abstain." Once we begin the vote, I will ask you to press the button that corresponds to your vote. After everyone has voted, the vote will then be complete.

The vote will be displayed on the screen and I will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state his or her name and the vote into the record, as well as the reason why they voted as they did.

The question on which we were asked to vote is the following. In view of the data

submitted for safety and efficacy, do you recommend approval of pegloticase for the treatment of refractory chronic gout? After we vote, we will have a number of other questions to discuss. Dr. Buckley?

DR. BUCKLEY: So we're going to vote on this approval really without a decision about for what population or studies. Is that what we're doing? So there's a number of unknowns on this vote.

DR. O'NEIL: Yes.

DR. ROSEBRAUGH: If I could just intercede. The way I would view this question is what would you personally do and then the other questions that follow it are your opportunity to define for us exactly what your vote meant.

The only other thing I might add, too, is that there is an abstain button, but that's really not one of the regulatory things that we have. So it would be nice if people didn't use the abstain button.

DR. O'NEIL: So try to fall on one side

of the fence or the other, if possible.

DR. ROSEBRAUGH: Well, it's called welcome to our world, we have to make a decision.

DR. O'NEIL: Yes. So I will read the wording again and you can see it on the screen. In view of the data submitted for safety and efficacy, do you recommend approval of pegloticase for the treatment of refractory chronic gout? And "yes," "no," and try to avoid "abstain."

The voting is complete and the results of the voting are 14 yes, one no, zero abstentions. We will now go around the room, and we'll start with Ms. Aronson.

MS. ARONSON: I voted no, and I'm being asked to discuss which additional data. I felt it wasn't --

DR. O'NEIL: Actually, no. You're just asked, at this point, to say no and why.

MS. ARONSON: Because there wasn't enough data on safety. So I could further -- do you want me to say further on that?

DR. O'NEIL: Briefly, sure. You're

welcome to.

MS. ARONSON: Okay, sure. I felt that if there were more information, more periodic information on blood pressure and electrocardiograms, that would have been helpful, and other blood -- liver enzymes, for instance, given the load of acetaminophen. And then more information about benefits versus risks of the long-term protocol, and then, specifically more about the elderly population.

DR. O'NEIL: Dr. Buckley?

DR. BUCKLEY: I voted yes, although, again, I don't know if you want comments. I think I would vote for limited use at this point, given the lack of long- term safety data.

DR. O'NEIL: Dr. Stine?

DR. STINE: I voted yes. I moved away from abstain under encouragement, but I think the discussion about the REMS and these subsequent strategies would be a very important proviso to go along with that yes.

DR. MIKULS: I voted yes, pretty much for

the reasons I previously stated in terms of an unmet need in a very needy patient population.

DR. O'NEIL: O'Neil. I voted yes, again, because of the unmet need, the fairly impressive efficacy, and the ability to try to put some limits on the use of this drug, which I think still needs to be further explored.

DR. OLSEN: Nancy Olsen. I voted yes because I do think that this drug would fulfill an unmet need.

DR. NELSON: Lewis Nelson. I voted yes, with the assumption that, at a minimum, we're going to go with the REMS recommended by the company.

DR. FURBERG: And I voted yes, reassured by the FDA leadership that you're going to take appropriate action to restrict use to the appropriate population and put in all the safeguards.

DR. WEISMAN: Michael Weisman. I voted yes because of the impressive efficacy for what was the orphan drug status and the ability of the

FDA to step up and to be able to do what we just heard that they're able to do.

DR. WILLIAMS: Jim Williams. I voted yes, because I felt that efficacy has been demonstrated and that there's a need for the drug.

DR. PACKER: I'm Milton Packer. I voted yes. The effects of this drug are so striking that they could be demonstrated in a small population and because of that, we can't be certain about the safety and that's going to be typical of drugs that have striking clinical benefits.

DR. KAUL: Sanjay Kaul. I voted yes. There is a fine line between a cautious yes and an abstention. I was actively discouraged away from abstention and reassured by what the FDA purported to be an enforceable REMS. Thank you.

DR. ROSING: Doug Rosing, and I voted yes, because I think there is a specific patient group that can safely benefit from this drug.

DR. O'NEIL: Dr. Neogi?

DR. NEOGI: Tuhina Neogi. I voted yes,

again, because of the unmet clinical need in this patient population, in whom the risks -- the benefit may be sufficient for the potential risk.

DR. O'NEIL: And, Dr. Clegg?

DR. CLEGG: Dan Clegg. I voted yes, for the unmet need.

DR. O'NEIL: Thank you. We are now asked, because the answer is yes, to discuss what additional studies, if any, should be conducted post-approval to further assess the safety of this product?

And who would like to volunteer to be the first speaker here? Oh, I knew it, Dr. Packer.

DR. PACKER: Although it would seem that there would be considerable enthusiasm for a registry, I have concerns that a registry like that would have significant limitations and would be hard to interpret. I'd like to think that having achieved what might be a limited approval for a focus population, that the sponsor might actually want to potentially expand its population to individuals who might appropriately be treated

with the usual xanthine oxidase inhibitors.

And so what I'd like to see is a randomized clinical trial of this drug versus a xanthine oxidase inhibitor long term in a meaningful number of patients.

DR. RAPPAPORT: Can I just make a clarification? Just so we're all on the same page here. There are two ways of looking at registry. One is a study, which is what you're talking about, to try to define the risk and your point is well taken.

The registry I was referring to in terms of a REMS is a mechanism for restricting to a certain population.

DR. O'NEIL: Yes, Dr. Weisman.

DR. WEISMAN: I think the type of registry that Dr. Rappaport has suggested, with a careful view of the population being exposed to this drug and follow-up of that population, I think will give a lot of useful information, on the one hand, and on the other hand, it gives us additional safety reassurance.

And so I would propose that that be -- that we let the FDA know that that's what we feel quite strongly about and that it should go forward. As far as restricting this drug to those patients who have already had an insufficient response to febuxostat, I don't think that's necessary, and I think that there are -- and I agree with Dr. Williams that it could be -- one could word it as "insufficient response to therapeutic doses" or "intolerant to either of the urate-lowering agents" would be appropriate, as far as I'm concerned, because there are going to be patients whose benefit should not be restricted.

Otherwise, I think I would leave the -- the term now is granularity of the discussion about whether -- about some of the issues involving the safety monitoring uric acid levels and so forth to further discussions between the sponsor and the experts within the agency to discuss.

I don't think we really should or have

the expertise to get into it here at this meeting. So those were the two suggestions that I'm making going forward, the type of registry that Bob Rappaport is discussing and not restricting it necessarily to failure of the -- complete failure of both of the urate-lowering drugs.

DR. O'NEIL: Dr. Nelson?

DR. NELSON: My earlier comment to address Dr. Rappaport's most recent statement actually was really directed exactly in that way, which is there are two different uses of the registry and I actually think we need both of those uses to be implemented here.

I think this idea of a post-marketing surveillance study use of a registry is very important to see what happens to patients. They threw out these numbers of 3,000 patients with a 50 percent increase in risk, et cetera, and I think those are numbers that you'll obviously decide what's best to do it.

But I think the other use of the registry that is actually somewhat more interesting to me

is to actually prevent patient harm, which would be to really -- their word, I think, was certification of the -- and whatever they're going to do with the patients who enroll, but really make sure that these are the right people to be in the study, make sure they have the right indication to get into the study and don't have the risk factors that would be concerning.

And if, over time, it needs to be liberalized or changed in some way, that's a decision that will be made, but I think, at the beginning, we have to be very clear that we're really going to introduce to this drug the patients who really are the ones we've talked about today.

I just am very concerned letting this out in the community. It may turn out to be wonderful, but given that we're still missing the denominator in a risk-benefit -- well, I guess the numerator in a risk- benefit analysis does concern me. So I think the registry concept is most important here.

In terms of additional studies, the one thing -- I know that some people have been fairly down on mechanism, but I do think that another mechanism I'd like to explore a little bit in a study perhaps would be the IgE mediated-ness of these infusion reactions, because if it's a true type one hypersensitivity reaction that's IgE mediated, it's an unusable drug in that patient population ever again. But if it's more -- and I may be using the wrong terms here, but if it's more anaphylactoid and it's related or there is some alternative administration strategy that will allow it to be used, I think that would be very important to know.

And it just seems like a piece of data. Maybe they have this information already. I saw the tryptase and all of that. And maybe that could be a explored a little bit further, because it does really impact pretty dramatically on patients' ability to get the drug in the long term.

DR. O'NEIL: Dr. Furberg?

DR. FURBERG: Well, I spoke up in favor of a registry and when I did that, I was thinking about a better design registry study. I don't like that about historical controls. They are not very informative.

So what I would like to see is a control group that is concurrent and, to the extent possible, matched in terms of risk, so you can get more information and have a more reasonable comparison.

The other thing I'd like to see, I support what Milton is saying, an active control study long term, I think, would be terrific. It would help us get more information both on efficacy, but maybe more safety. And the third possibility whether the sponsors is introducing the drug in other countries. It's possible that you can get with a placebo control study in other countries for ethnical reasons. I don't think you can do that in the U.S. any longer.

DR. O'NEIL: I was going to ask you who the control would be.

DR. FURBERG: Well, as I said, you have people with treatment resistant gout, the population we are talking about here that we're approving the drug for, and select them concurrently as you do the registry and try to match that, and that's how I would do it.

DR. O'NEIL: Dr. Williams?

DR. WILLIAMS: I had two points. One, I was one of the original enthusiasts for a registry, but Dr. Packer has convinced me the error of my ways. But I do think that there should be some type of long-term evaluation for safety.

Secondly, I'm very concerned that we not consider inadequately treated gout refractory gout. I don't know if you can limit it to nephrologists or rheumatologists, but I think that we ought to make sure that inadequately treated gout isn't considered refractory gout.

DR. RAPPAPORT: Can I just ask for a clarification? A couple of people have said long-term studies. What time frame are you

thinking?

DR. WILLIAMS: You probably have more experience with that than we do, but I would think that you would -- it would be nice if you had a five-year study on patients who had been on this drug and what happens to them.

That's just my opinion, but I think that you need to -- there are enough concerns, particularly about cardiovascular disease and with the experience we had with the NSAIDs, I just think that we need to find out if this is just a sign or if it's just an at risk population.

DR. O'NEIL: Dr. Olsen?

DR. OLSEN: I was just thinking the control group is a good idea, but it's going to be hard to discuss this with people who are aware that this drug is out there. I wonder if an alternative, it's not exactly randomized control group, but would be you'd offer it to people who decided they didn't want to take the risk. Then would they be willing to go into a control group that's just followed on their usual therapy? That

might more rapidly accrue a control group.

DR. O'NEIL: Ms. Aronson?

MS. ARONSON: My lay perspective on developing risk management. I'm just wondering about the objectivity and the subjectivity and choosing who might go into some of these, some treatment. I'm just wondering, is there ever an algorithm that's developed so that things can be punched into a computer on what treatment has transpired.

DR. O'NEIL: For that, we'll let Dr. Stine weigh in.

DR. STINE: My comment would be looking forward to other sorts of medications, as was pointed out before, that are so efficacious that you can prove efficacy with a small study, we had our chance, guys, to have the randomized clinical trial for safety. We had that. You either get that now or you don't get it.

You can say whatever you want about coming up with some computer algorithm that's going to do it post hoc, but it's not going be the

same thing. And I think looking ahead toward other drugs, we're going to have to think more about getting the safety data in the first place, along with efficacy, or we're going to be stuck in this same situation again and again and again.

And I don't know that it could have been anticipated this time, but I think this whole issue of the registry now, we're not going to have some magical randomized clinical trial in that registry. I think there's just so many impediments to that, it's just going to be very, very difficult to see that happen.

DR. O'NEIL: So to be a bit more specific, what would you like to see happen?

DR. STINE: A randomized clinical trial for safety. I just don't see how that's going to be manageable once you get it out there. If we approve this drug for that, how are you going to talk to somebody that's got these tophi and in this kind of pain that, "Oh, I'm going to randomize you to something that's probably not going to help you." I find that a very, very

difficult position t put somebody into, frankly.

DR. O'NEIL: Dr. Buckley?

DR. BUCKLEY: Well, I think one possibility might be a randomized clinical trial where people who have felt they're not responding would be continuing on a drug that they may be not fully responding to, like allopurinol or febuxostat.

They have a partial response or no response versus having this drug. So not no treatment at all, but continuing a drug that you might think is -- to which you've only had a partial response.

DR. STINE: All I was going to say then is then you don't have the randomization now, because you're going to be selecting on some other characteristic as to who gets treatment and who gets control.

DR. BUCKLEY: If you were to take everyone who was on -- felt that they had inadequate control and offer them either to continue what they're doing, which is not no

treatment usually or to move on to this other treatment, you would at least have -- you'd be able to compare it to a baseline treatment.

DR. O'NEIL: Dr. Kaul?

DR. KAUL: I endorse the restricted indication registry, which is enforceable. With regards to the registry, I am not too enthusiastic about the registry data simply because it will be very difficult to dissect out the signal.

If we are to do a randomized clinical trial, I agree an active control would be a proper design, but we haven't had any discussion about what degree of clinically important harm and cardiovascular events are we going to exclude in that clinical trial.

I heard 50 percent as a degree of tolerable inferiority and I am pretty much taken aback by that, such a generous margin of non-inferiority. Here's a drug which, no doubt, is effective, but it is to be infused every two weeks or every four weeks and is going to be very expensive.

I don't think I'm prepared to tolerate a 50 percent loss or the margin of non-inferiority. And if we were to choose an appropriate perhaps 15-20 percent, what are the consequences on the sample size of that particular trial?

I think we haven't had any discussion with regards to that. So I think I believe in a pragmatic approach, the most pragmatic approach here is to have an enforceable restricted patient registry, if it can be done, and kudos to the FDA if they can do it, and perhaps think about what sort of a study are we talking about in terms of the randomized clinical trial.

DR. O'NEIL: Dr. Packer, briefly.

DR. PACKER: Gee, 50 percent seems pretty good. An upper bound of 1.5 would still result in an enormously large trial. And I don't know anyone who has ever required an upper bound of 1.15 or 1.2, realizing that 1.5 would give us a lot more information than we have now. Frankly speaking, two would give us a lot more information than we have now.

DR. KAUL: But it's an intravenous drug and more expensive. So you have to consider that, as well.

DR. PACKER: Why? Why?

DR. KAUL: What are the ancillary advantages of this drug to warrant a narrow non-inferiority margin? I mean, that certainly has to have a bearing in the choice of the margin.

DR. PACKER: But the question is what's the upper bound of the cardiovascular risk, that's the only question that's relevant to the sample size.

DR. KAUL: Regardless, I agree with you that the sample size is going to be prohibitive, whether it's 50 percent, and, ideally, narrower than that, 25 percent.

DR. O'NEIL: Dr. Buckley?

DR. BUCKLEY: I would also like -- we're looking at what is treatment failure gout. I would add the oral agent febuxostat. I don't have all the data here about their long-term safety, but I think, given the potential cost and the

potential toxicity and mostly our limited safety data, I would say treatment resistant gout is gout where these two agents have been tried or there is a contraindication to one or both in a patient who is compliant with those treatments.

DR. O'NEIL: Dr. Neogi?

DR. NEOGI: Just focusing on question A, additional studies, I think there are some -- in addition to the cardiovascular safety we've been discussing, I think some of the other unknowns are dialysis patients, transplant patients. I think those studies need to be done, because that's another unmet -- a population with unmet needs.

And I think we've already discussed the issue of long-term maintenance. What do we do with these patients after -- so this drug is out on the market, they've had it for 12 months, and then what do we do?

So we do need additional studies for further guidance on management.

And this issue of the registry, I think, I agree that it's an important initiative to have

the registry to try to limit the patients that are receiving the medication and I agree that it's going to be excessively difficult to assess safety.

A VA population you're not going to be able to match on the severity of the same type of treatment refractory gout patients that you are enrolling in your studies. It will be very difficult to get a proper control group, as people have said, when the drug is already out there and available.

A randomized trial with febuxostat, which already has a safety signal there, is going to -- even if it's no different than febuxostat, we've still not answered whether there's an increased risk. So I think the cardiovascular safety issue is going to be exceedingly difficult to come to a conclusive satisfactory answer.

And the other additional study I think would be to study the use of this drug in persons who have been optimized on their therapies. So apart from the hypersensitivity, we still haven't

gotten a good sense of what dose people are on for allopurinol, how many could have been on probenecid, and now that febuxostat is out there, so in the context of clinically available drugs.

DR. O'NEIL: Dr. Mikuls?

DR. MIKULS: In terms of registry, I guess I'm a little less pessimistic than my cardiologist colleagues. I don't necessarily see a way around them. So I understand that the cardiovascular events, as you just said, are going to be very difficult in the end to -- but I do think there's still the question, as Dr. Furberg mentioned, long-term safety issues that may not arise in the first six months of use.

There's also the other major serious adverse events seen were the infusion reactions and I think a registry does offer us a mechanism to perhaps mitigate against that. So has the proposal put forward by the sponsors of taking folks out who get a serum urate above six, is that going to work?

Well, we know it worked in the RCTs for,

I think, 17 of 19 patients. Is that going to work among the bigger patient population? Are there better strategies at preventing or prophylaxing against infusion reactions? That sort of thing is going to come out of registry, I believe.

So I would endorse a registry with those questions in mind and I also would endorse an enforceable REM.

DR. O'NEIL: I think one other question that has already begun to be addressed in your trial C0409, I believe, or your follow-up study, long-term follow-up study, is in individuals in whom this immunogenic drug is discontinued, what are the risks of retreatment, and I think that's a very important question that I would like to see more data on in the future. I think that's very important.

Dr. Buckley?

DR. BUCKLEY: I think to add to that, this long-term issue is when a patient comes off treatment, how likely are they going to need to get back on treatment. And if we're hypothesizing

that maybe this would be a period of induction with this drug and then they would go on to pegloticase, probably not allopurinol, but does that work?

I think that's an important thing to know. We know only that it's temporarily helpful, but its long- term impact and what the transitional drugs will be in the long-term, I think, is an important question to answer.

DR. O'NEIL: So you're suggesting that there may be a real niche for this drug and debulking the uric acid load in a body and then perhaps another relatively more effective drug, like febuxostat --

DR. BUCKLEY: Might then be able to keep the urate load down.

DR. O'NEIL: -- might maintain adequate.

DR. BUCKLEY: And I think if the company is saying, "This is a drug we're going to suggest for use for a year," then there's a big question mark. What comes after that year? And I think that that issue needs to be taken on. Is it

retreatment? Is it moving to other treatments? Is it a combination of both of those or will the answer be different for different kinds of patients?

DR. O'NEIL: And I have one quick immunology question, if I might ask. I think probably Dr. Lipsky is the person to whom I should direct this. With the individuals who had high antibody titers and maintained relatively high uric acid levels over time, despite being treated with active agent, was there any evidence over time of a tolerance being induced to this drug?

DR. LIPSKY: Unfortunately, no. But again, the amount of data collected in the open label extension wasn't as extensive to conclusively answer that question. But it appears to be no, from the first look.

DR. O'NEIL: Thank you. Is the FDA sufficiently saturated with the variety of responses to this question? I guess Dr. Williams has one more comment.

DR. WILLIAMS: We haven't addressed

Dr. Packer's question about when you should tell people that they're at risk for an immune reaction because their uric acid is going back up.

If you take six and half of the people are below six, how do you determine that?

DR. O'NEIL: Are you going to answer that, Dr. Buckley?

DR. BUCKLEY: I wanted to comment on it. And I think, also, there question, is it a set level or is it a change, is it a rate of change that will trigger that decision.

DR. O'NEIL: I'm afraid, without examining the individual data points and the individual trends, it's going to be very hard for any of us to make a guess at that, and I think we will have to leave that to the statistics people at the FDA and the company.

DR. WILLIAMS: I don't think we have data to answer it, but I think it's something the FDA needs to think about. If they're going to make the proposal that at six, we tell people -- that people go back to six, we stop it, is that the

correct number.

DR. SIEGEL: I think the question is how patients should be monitored and at what level of uric acid, what time point you would stop treating patients because of the risk of infusion reaction later on.

I can imagine a number of different approaches you could use, some kind of receiver operating curve for uric acid as a predictor of later infusion reactions. This is certainly something that we can explore, but it's the issue of what the optimal cutoff is and we can certainly explore what different ones -- how different ones would perform.

DR. O'NEIL: Those are issues that I think we all think need to be addressed. The next question we're asked to address is to discuss the appropriate patient population for whom pegloticase should be indicated. Dr. Williams?

DR. WILLIAMS: I think we've kind of mixed that in with all of our other discussion and my thought is it should -- refractory gout would

be fine, but not inadequately treated gout.

DR. O'NEIL: And how to enforce that is going to be a difficult issue.

DR. PACKER: I have a question to the rheumatologist. Would you give this drug to someone who had uric acids of 12 -- I'll make that up -- who had one episode of gout years ago and couldn't take allopurinol? In other words, clinically mild gout, no tophi.

DR. WILLIAMS: I can only answer for one rheumatologist, but I don't treat the first attack of gout chronically, because it may be years until they have the second attack of gout.

Now, once they've had the second attack, the third attack will probably be in a lesser time. And so if the time level is sufficient, then we treat them with allopurinol. But I would never treat -- I would not use pegloticase as a first choice for any gout patient.

DR. PACKER: I guess what I'm asking is is there a -- does the term refractory gout mean something that rheumatologists would -- I can see

where everyone would say, "Gee, if the person had tophi and renal failure and painful joints and all of these things," if someone didn't have any of those things, but had refractory hyperuricemia, would they get the drug?

DR. O'NEIL: We'll let Dr. Williams continue to treat Dr. Packer.

DR. WILLIAMS: We don't treat asymptomatic hyperuricemia. So I personally don't treat asymptomatic hyperuricemia. Now, if they develop tophi or renal stones or gout or arthritis, then you would treat that. But to me, refractory gout means they have not responded to adequate doses of allopurinol or febuxostat -- and/or febuxostat. I think you could make the case for either one.

DR. O'NEIL: Dr. Furberg?

DR. FURBERG: I have problems with the question. I don't know how we can discuss another population beyond the refractory, because we have no data. We can't approve drugs for a population where we have absolutely no information.

DR. O'NEIL: Dr. Weisman?

DR. WEISMAN: I think the orphan drug status of this application answers the question.

DR. O'NEIL: Thank you. Any further discussion on this issue? Dr. Packer, if you could turn off your light, please.

DR. OLSEN: So specifically, in view of that, then that doesn't mean that the patient would have to have failed febuxostat, because that wasn't the population that was looked at here. So I wouldn't see that -- I would think you'd have to start with what you know and what you know is this population.

Some of these patients, had that been available, would have been treated with that other drug. So I think you'd now say, well, you could get either depending on what's going on, what the other issues are.

DR. O'NEIL: I think one other point, though, is that there appeared to be a niche particularly for people with very bulky tophaceous gout and these individuals may indeed not need to

be put on febuxostat first.

DR. WILLIAMS: I was not here for the previous meeting on febuxostat, but I would think that since they work similarly, that I said allopurinol or febuxostat. Some people have said and/or or and, but I think you could use either one and say that if they failed a xanthine oxidase inhibitor, that they then had refractory gout.

DR. O'NEIL: As one who was here for that meeting, I can just advise you that febuxostat does not need adjustment for renal clearance, and that's one of the big differences. Dr. Weisman?

DR. WEISMAN: We're not talking about treating inter-critical gout here. We're talking about treating critical clinical gout and that I don't -- most rheumatologists know exactly what that means.

DR. O'NEIL: Which I think implies that perhaps restricting those who prescribe the drug may be important, because I'm not sure we want every family practitioner in Oklahoma prescribing this drug without supervision. And I can say

that. Dr. Mikuls?

DR. MIKULS: So the case for adding febuxostat to the refractory gout, there can be -- there certainly could be a case made for that, regardless of the fact that that wasn't the patient population studied.

The case would be that there are patients who have gotten into these studies on, quote, "suboptimal therapy" for allopurinol. We've all had these patients. They had a creatinine of two. And so someone looked in the PDR and they got a 100 milligrams of allopurinol a day, it was never dose escalated, and that gets termed refractory gout.

Many of us would argue that that's not refractory gout. Since febuxostat now has a label that doesn't need to be renally dose adjusted, those patients could be tried on febuxostat, at least theoretically, although there's limited data with really impaired renal insufficiency, I don't think any patients with a creatinine over two.

But that would be at least a theoretical

case I could make for including that in the refractory gout population. Very easy argument to make.

DR. O'NEIL: All right. Thank you. I think we're going to move on to part C here, which is to discuss how patients treated with pegloticase should be monitored, how frequently should uric acid levels be followed, et cetera. Dr. Williams, you woke up after lunch.

DR. WILLIAMS: I have no reason to disagree with the sponsor. I think that for the first three months, you ought to get a uric acid with each one, since they seem to have pretty compelling data that if they lose control, they then are at higher risk for immune reactions.

So I would do it every infusion for the first three months. After that, I don't think we have any data to support it for perhaps every three months.

DR. CLEGG: It seems like the data will have to be looked at more clearly, but it also appeared that maybe change in uric acid from the

determination before might be as important or more important than the absolute value.

DR. O'NEIL: Dr. Mikuls?

DR. MIKULS: So there's a quality indicator out there that patients who start allopurinol or urate- lowering therapy should have serum urates done within six months of starting a therapy, which is pretty generous. About probably less than a third of physicians do that who are treating gout.

So I believe, based on the data, that it should be done with the infusion. But part of the follow-up needs to be looking at the question is that being done, what's the adherence with that, how can we prove adherence with that, if we believe that it's important.

DR. O'NEIL: Dr. Weisman?

DR. WEISMAN: I agree with the sponsor about monitoring. I think the more we make this somewhat restrictive and not for the faint-hearted, that I think we're going to get a better outcome and I think that the issue

involving the relationship with the serum uric acid and side effects is still a open question and I think we need to know the answer to that. So I would recommend the way the sponsor has done the initial trial.

DR. O'NEIL: Is there further discussion on this point? Thank you. Are there other questions the FDA would like the panel to address?

DR. SIEGEL: No, I don't think so.

DR. O'NEIL: I'd like to thank everyone for their participation and thank FDA.

DR. SIEGEL: On the part of the FDA, we would also like to thank the panel very much for their efforts. We know that some of these questions are very difficult, especially in terms of restricting patient populations and getting more long-term data. Thank you very much.

[Whereupon, at 3:26 p.m., the meeting was concluded.]